http://dx.doi.org/10.5935/0103-5053.20140103

J. Braz. Chem. Soc., Vol. 25, No. 7, 1253-1260, 2014.
Printed in Brazil - ©2014 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Efficient Synthesis of Novel Pyranoquinoline Derivatives from Simple Acetanilide Derivatives: Experimental and Theoretical Study of their Physicochemical Properties using DFT Calculations

Zohreh Mirjafary,[a] Hamid Saidian,[b] Morteza Sahandi[b] and Leila Shojaei[b]*

[a]*Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran*

[b]*Department of Science, Payame Noor University (PNU), PO Box 19395-4697, Tehran, Iran*

Uma reação conveniente para sintetizar piranoquinolinas úteis a partir de derivados de 2-cloroquinolina-3-carbaldeído e dimedona na presença de KF-Al_2O_3 é descrita. Rendimentos razoáveis (41-50%), matérias-primas facilmente encontradas e catalisador eficiente pouco caro são os destaques deste método. Foi proposto um mecanismo de reação. A atribuição dos deslocamentos químicos foi feita com ajuda de cálculos de teoria do funcional da densidade (DFT). Os deslocamentos químicos de ressonância magnética nuclear (NMR) calculados têm boa concordância com dados experimentais. Valores de deslocamento químico independente de núcleo (NICS) foram usados como medida quantitativa do caráter aromático relativo de piranoquinolinas. Os valores calculados de NICS do grupo fenila de compostos piranoquinolínicos são menores que aqueles do benzeno.

A convenient reaction of 2-chloroquinoline-3-carbaldehyde derivatives and dimedone in the presence of KF-Al_2O_3 for the synthesis of useful pyranoquinolines is described. Reasonable yields (41-50%), easily available starting materials and less expensive efficient catalyst are the key features of the present method. A mechanism was proposed for the reaction course. Attribution of the chemical shifts was made with the help of the density functional theory (DFT) calculations. The computed nuclear magnetic resonance (NMR) chemical shifts are in good agreement with available experimental data. The nucleus-independent chemical shift (NICS) values were used as quantitative measures for the relative aromatic character in pyranoquinolines. The calculated NICS values obtained for the phenyl group of pyranoquinoline compounds are smaller than that of benzene.

Keywords: quinoline, pyranoquinoline, Knoevenagel condensation, aromaticity, DFT calculations

Introduction

The quinoline nucleus comprises a class of heterocycles, which has been exploited more immensely than any other nucleus for the development of potent drugs. A range of pharmacological properties, such as antibacterial, antitumor, anti-inflammatory, antimalarial, antioxidant, antimicrobial and antifungal activities of this important class of heterocycles are found in the literature (Figure 1).[1] Additionally, quinoline derivatives find use in the synthesis of fungicides, biocides, alkaloids, rubber chemicals, flavoring agents and as antifoaming agent in refineries.[2] On the other hand, pyran derivatives possess a wide-range spectrum of biological activities including antiviral, antitumor, and mutagenicity activities.[3] However, an extensive literature survey reveals that sufficient efforts have not been made to combine these heterocycles, pyranoquinolines, in the same molecular scaffold.[4] Pyranoquinolines possess a wide range of interesting biological activities, such as anti-allergic, anti-inflammatory, psychotropic, and estrogenic activities.[5] Thus, the development of an efficient method for their synthesis still attracts much interest.

KF-Al_2O_3 was introduced by Clark as a solid base and has been applied as catalyst to a wide variety of organic synthesis. Several recent articles have reviewed this field.[6] The strongly basic nature of KF-Al_2O_3 allows it to replace organic bases in a number of reactions. In the context of our general interest in the synthesis of heterocycles,[7] herein, we

*e-mail: h_porkaleh@yahoo.com

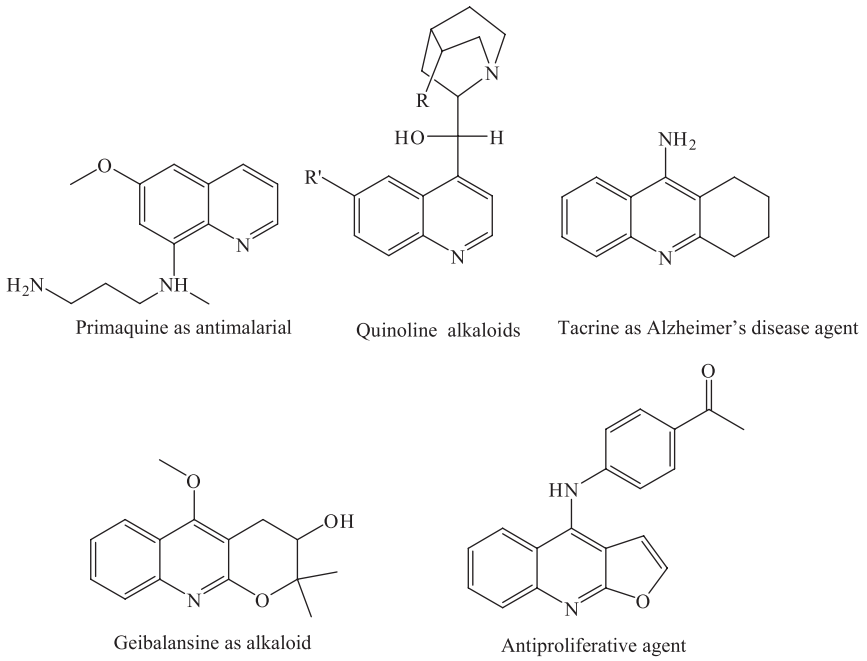


Figure 1. Some quinoline-containing bioactive compounds.

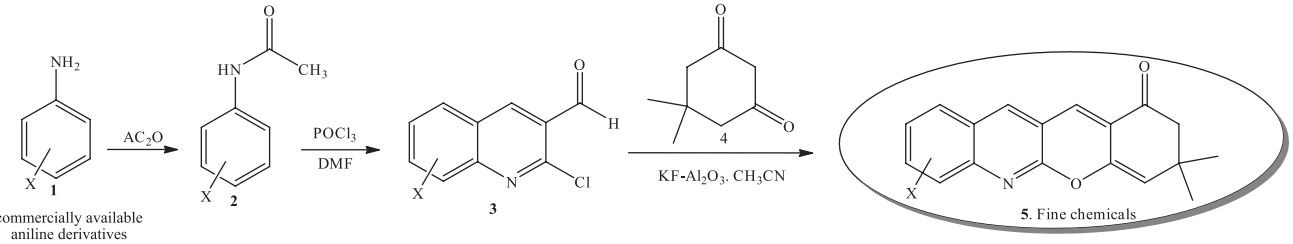
propose a facile synthesis of pyranoquinoline derivatives **5** using KF-Al_2O_3 as an efficient, commercially available and non-toxic catalyst (Scheme 1). Good yield and low cost of the reagents are the salient features of this method. The reaction starts from easily accessible starting material, which makes it an interesting process for the preparation of pyranoquinolines **5**. 2-Chloroquinoline-3-carbaldehyde derivatives are very useful starting material for synthesis of a wide variety of heterocycles[8] and can be easily synthesized from acetanilide derivatives with Vilsmeyer-Haack reaction.[9]

Additionally, a combination of experimental and density functional theory (DFT) calculations was also used to investigate their physicochemical properties, such as nuclear magnetic resonance (NMR) data, and aromaticity. It was shown that DFT methods perform NMR spectra calculations very well and give accurate results.[10] On the other hand, aromaticity is a vital property of conjugated cyclic molecules in the determination of their structure, reactivity, and stability. Aromaticity is not a directly measurable or computable quantity.[11] Among the magnetic criteria, nucleus-independent chemical shift (NICS) continues to gain popularity as an easily computed, generally applicable criterion to characterize aromaticity and antiaromaticity of different compounds.[12] NICS is computed as the negative magnetic shielding at selected points at the ring center, above or below the ring. Negative NICS values indicate aromaticity, whereas positive values indicate antiaromaticity, and small values represent non-aromaticity. It is recommended that the NICS(1) (at points 1 Å above the ring center) to be the best measure of the π-electron delocalization in a cyclic molecule.[13] In this paper we use NICS as quantitative measures for aromatic character in pyranoquinolines **5**. The ^{1}H NMR and ^{13}C NMR chemical shifts of pyranoquinolines (**5a**) were also determined by DFT calculations with the help of full spectral analysis.

Experimental

General information

All chemicals required for the synthesis of pyranoquinolines **5** were purchased from Fluka (Neu-Ulm,



Scheme 1. Efficient synthesis of pyranoquinolines.

Germany), Sigma-Aldrich (St. Louis, MO, USA), and Merck (Darmstadt, Germany) and were used as received. The KF-Al_2O_3 support was prepared according to previously reported procedure.[6] The synthesized compounds **5** all gave satisfactory spectroscopic data. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Gas chromatography-mass spectrometry (GC-MS) (Agilent HP 6890, electron ionization (EI), 70 eV, HP-5 column (30 m × 0.25 mm × 0.2 μm), HP 5793 mass selective detector) was used to record the mass spectra.

Computational methods

All geometry optimizations and frequency calculations of all species were carried out using the Gaussian 03 program.[14] Density functional theory with the Becke three parameters hybrid functional (DFT-B3LYP) calculations were performed with a 6-31+G(d,p) basis set. Vibrational frequencies were calculated at the same level to ensure that each stationary point is a real minimum. Harmonic oscillator approximation was also used for the thermodynamic partition functions. After geometry optimization and frequency calculations, zero-point energies (ZPEs) and thermal corrections were obtained at 298 K. The NMR computations were performed using the gauge-independent atomic orbital (GIAO) and continuous set of gauge transformations (CSGT) methods.[15] NICS values are calculated at 1 Å above the plane of the optimized compounds, NICS(1), using the GIAO method at B3LYP/6-31+G(d, p).

General procedure for synthesis of acetanilide **2**

To a solution of 60 mL water and 8 mL aniline (0.08 mol) were added 10 mL acetic anhydride (0.1 mol). The reaction mixture was stirred at 40-50 °C for 30 min. After completion of the reaction, the mixture was poured into ice-cold water and stirred for 10 min, which resulted in precipitation of acetanilide **2**. The solid precipitate was filtered, washed with 30 mL of cold water, and then dried.

General procedure for synthesis of 2-chloroquinoline-3-carbaldehydes **3**

To stirred DMF (3.6 mL, 46 mmol), 12.5 mL $POCl_3$ (134 mmol) were added dropwise at 0-5 °C. The mixture was allowed to stir for 30 min. Acetanilide **2** (18.5 mmol) was then added and the resulting solution heated for 12 h at 80-90 °C. The mixture was poured into ice-cold water and stirred for 10 min, which resulted in yellow precipitation of the desired 2-chloroquinoline-3-carbaldehydes **3**. The precipitate was filtered and washed with water and then dried. The compounds were purified by recrystallization from ethyl acetate.

General procedure for synthesis of pyranoquinolines **5**

To a stirred suspension of 100 mg KF-Al_2O_3 in acetonitrile (5 mL) were added 2-chloroquinoline-3-carbaldehyde **3** (1 mmol) and dimedone (140 mg, 1 mmol). The reaction mixture was stirred at 80-90 °C for 10 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the solvent was removed under reduced pressure, and the residue was separated by preparative TLC (eluent: petroleum ether/ethyl acetate 5:1) to afford the desired compound **5**.

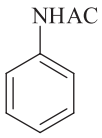
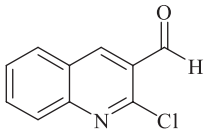
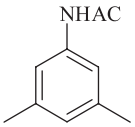
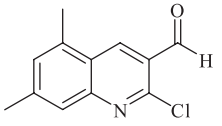
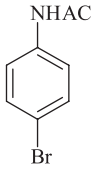
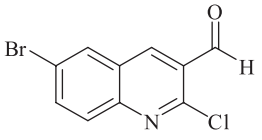
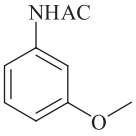
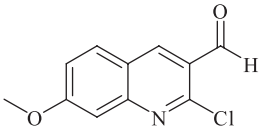
Results and Discussion

Synthesis

The 2-chloroquinoline-3-carbaldehyde derivatives **3** were prepared from the corresponding substituted acetanilide **2** and Vilsmeyer-Haack agent (DMF + $POCl_3$) with high yields and excellent purity at 80-90 °C (Table 1).

To find the optimal conditions for the synthesis of pyranoquinolines **5**, reaction of 2-chloroquinoline-3-carbaldehyde **3a** and dimedone **4** in the presence of a base was chosen as a model reaction. A mixture of **3a** (1 mmol), dimedone **4** (1 mmol), and solvent (5 mL) was stirred under various reaction conditions. Our first experiment showed that the presence of a base such as K_2CO_3 or KF-Al_2O_3 is required to achieve the synthesis of **5a**. K_2CO_3 was less effective compared to KF-Al_2O_3. We then continued to optimize the model reaction by considering the efficiency of polar and nonpolar solvents. A polar solvent such as CH_3CN was much better than a nonpolar solvent. The effect of temperature was also studied by carrying out the model reaction at room temperature and 80-90 °C. It was observed that the yield was increased as the reaction temperature was raised to 80 °C. The structures of the products were confirmed by EI-MS, ^{1}H NMR, and ^{13}C NMR analysis (see Supplementary Information). The ^{1}H NMR and ^{13}C NMR spectra of the product clearly indicated the formation of **5a**. The characteristic signals for **5a** in the ^{1}H NMR spectra were a singlet for the protons of methyl groups at 1.22 ppm, a singlet for CH_2 protons of dimedone ring at 2.56 ppm, and a doublet signal for the vinyl proton of the dimedone ring at 5.54 ppm. The presence of this signal in

Table 1. Synthesis of 2-chloroquinoline-3-carbaldehyde derivatives **3**

entry	Acetanilide **2**	Product **3**	Yield / %
1		 **3a**	89
2		 **3b**	86
3		 **3c**	74
4		 **3d**	83

the ^{1}H NMR spectra of the synthesized compounds is a good indication of the formation of the desired compounds. A sharp and deshielded signal for the vinyl proton of pyran at 7.21 ppm and five peaks for the aromatic protons at 7.22-7.88 ppm are the other characteristic signals in the ^{1}H NMR spectrum of **5a**. The ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT) 135 spectra of **5a** showed 17 distinct resonances in agreement with the proposed structure, at δ = 196.56 ppm resonance for the carbonyl carbon, 13 distinct resonances for aromatic and vinylic carbons between δ = 116.25-159.08 ppm, a resonance at δ = 53.18 ppm for the methylene carbon, a resonance at δ = 33.42 ppm for the quaternary carbon of dimedone and a sharp resonance at δ = 30.51 ppm for the carbons of methyl groups. EI-MS spectrum of **5a** clearly showed the presence of the molecular ion ($M^{+\bullet}$, *m/z* 277) with relative high abundance and other expected fragments. Direct elimination of methyl moiety from $M^{+\bullet}$ yielded ion at *m/z* 262 as base peak in EI-MS spectrum. This fragment can be stabilized by the aromatic system (Scheme 2).

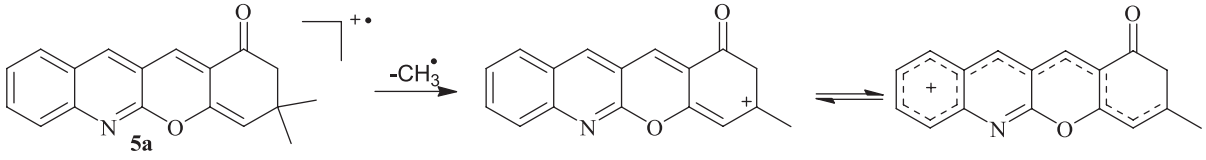
To generalize this method, we used a series of 2-chloroquinoline-3-carbaldehyde derivatives to obtain their corresponding pyranoquinolines **5** (Table 2). As shown in Table 2, all the substrates consistently underwent reaction to the desired pyranoquinolines **5** in moderate yields.

A plausible mechanism for the present reaction to produce pyranoquinolines **5** is proposed in Scheme 3. In the first step, dimedone can undergo a Knoevenagel condensation with 2-chloroquinoline-3-carbaldehyde **4** in refluxing CH_3CN to afford the intermediate **I** with the release of H_2O. Subsequently, the ring closures proceed through an addition-elimination reaction to give the desired pyranoquinolines **5** under reaction conditions.

Computational results

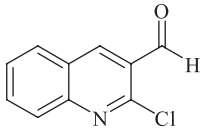
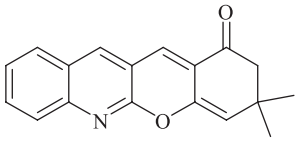
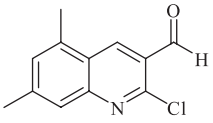
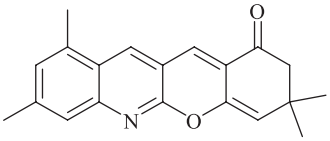
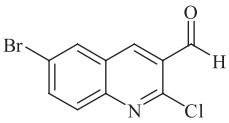
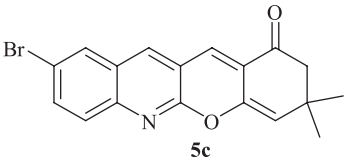
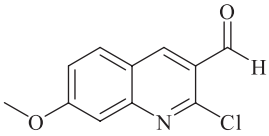
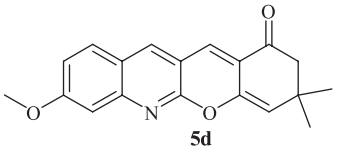
NMR calculations

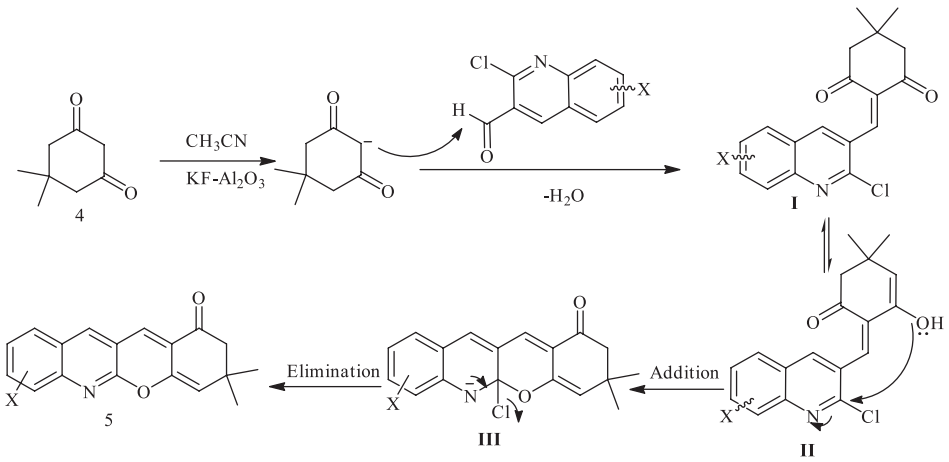
Atom numbering in accordance with molecular structure of pyranoquinoline **5a** is given in Figure 2. A main important goal of this part is to properly assign



Scheme 2. Stabilization of ion at *m/z* 262 as base peak by the aromatic system in EI-MS spectrum.

Table 2. Synthesis of novel pyranoquinolines **5**

entry	2-Chloroquinoline-3-carbaldehydes **3**	Pyranoquinolines **5**	Yield / %
1	 **3a**	 **5a**	50
2	 **3b**	 **5b**	46
3	 **3c**	 **5c**	44
4	 **3d**	 **5d**	41



Scheme 3. Possible mechanism for the formation of novel pyranoquinolines **5.**

the experimental NMR data to the computed data of **5a**.

At first, the geometry of the molecule was optimized. After that, ^{1}H NMR and ^{13}C NMR chemical shifts calculations were performed using B3LYP/6-31+G(d,p). Chemical shifts were reported in parts *per* million relative to tetramethylsilane (TMS) for ^{1}H NMR and ^{13}C NMR spectra. Relative chemical shifts were calculated by using the corresponding TMS shielding calculated at the same theoretical level as the reference. The relations between the

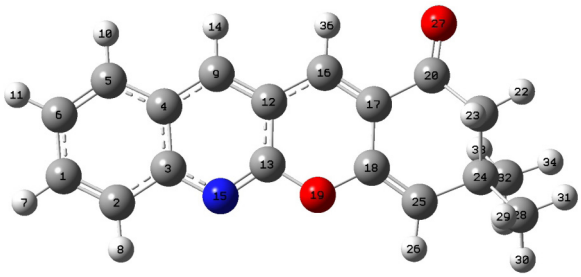


Figure 2. Atom numbering in accordance with the molecular structure of pyranoquinoline **5a**.

experimental ^{1}H and ^{13}C chemical shifts (δ_{exp}) and magnetic isotropic shielding constants (δ_{calc}) are usually linear and described by the following equation: $\delta_{exp} = a + b\ \delta_{calc}$. The slope and intercept of the least-square correlation are utilized to predict chemical shifts. The relative ^{1}H and ^{13}C chemical shifts were calculated by two methods: Gauge-Independent Atomic Orbital (GIAO) and Continuous Set of Gauge Transformations (CSGT) (Table 3). According to the comparison between experimental and calculated data, the calculated ^{1}H chemical shifts are in acceptable agreement with the experimental results obtained by the GIAO method. The determination coefficient for proton chemical shifts in GIAO method is determined to be 0.9976 as shown in Figure 3.

Table 3. Representative computed B3LYP/6-31+G(d,p) ^{1}H and ^{13}C chemical shifts for pyranoquinoline **5a** (see Supplementary Information)

Atom	Theoretical chemical shift / ppm		Experimental chemical shift / ppm
	GIAO	CSGT	
H14	7.54	5.71	7.88
H22	2.26	1.21	2.56
H26	5.57	3.99	5.54
H29	1.19	0.48	1.22
H36	7.18	5.06	7.21
C20	190.77	194.79	196.56
C21	53.54	55.22	53.18
C24	36.46	34.41	33.42
C28	30.65	32.15	30.51

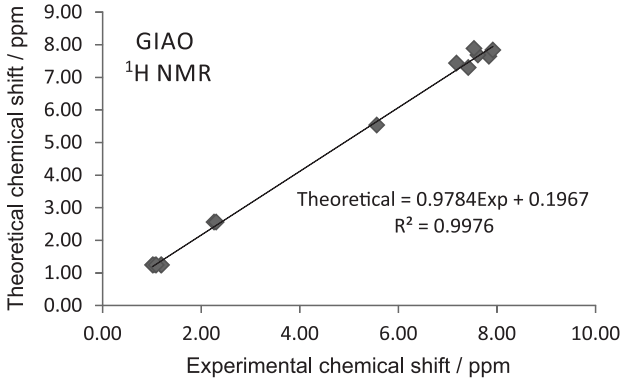


Figure 3. Determination coefficient for ^{1}H chemical shifts in GIAO method for pyranoquinoline **5a.**

Aromaticity calculations

This study also includes benzene molecule calculations for comparison and study of the addition effect of the ring on the aromaticity properties (NICS) of benzene. The results show that NICS for the phenyl group of pyranoquinoline compounds **5** are less than that for benzene, as expected (Table 4). An account for the decrease of the aromaticity in such systems is lower resonance energies *per* π electron than benzene. Their values are close to the ideal aromaticity index (NICS(1) = −10.2 ppm) stated by the NICS model for benzene.

Table 4. NICS values for the phenyl group and summation of the NICS (NICS(1) and ∑NICS(1), respectively) at 1 Å above the phenyl group of pyranoquinoline systems **5** calculated at GIAO- B3LYP/6-31+G(d,p) level

Pyranoquinoline **5**	NICS(1)	∑ NICS(1)
5a	−9.8937	−15.0573
5b	−9.1881	−13.9780
5c	−9.4087	−14.6380
5d	−8.9147	−13.4848

Interestingly, the aromaticity of the phenyl group of pyranoquinoline systems **5** was deeply affected by substitution. Generally, substitution decreases the aromaticity of the phenyl group of pyranoquinolines **5** compared to benzene. NICS values predict decreasing and increasing effects for the electron donating group (such as OCH_3, with NICS(1) = −8.9147 ppm, Table 4, entry 4) and electron withdrawing groups (such as Br with NICS(1) = −9.4087 ppm, Table 4, entry 3), respectively.

It should be mentioned that the NICS index does not allow the aromaticity of a polycyclic conjugated system like pyranoquinoline systems **5** to be estimated directly. On the other hand, it is not easy to know how to use NICS values for different ring systems to handle a global property like aromaticity. Schleyer *et al.*, in 2001, introduced the summation of the NICS values as a global aromaticity index.[16] As a result, the summation of NICS values for a given polycyclic system produces a single quantity called the "total NICS". Therefore, in this study the sum of the NICS calculated at 1 Å above the rings, ∑ NICS(1), is also used to evaluate the aromaticity of each molecule as a whole (Table 4). As shown in Table 4, substitution decreases the aromaticity of pyranoquinoline systems **5** and the unsubstituted pyranoquinoline **5a** is proposed as the most aromatic compound among 4 species. On the other hand, methoxide as an electron donating moiety decreases the aromaticity of pyranoquinoline **5d**.

Conclusions

In summary, we have described a simple and efficient protocol for the synthesis of novel pyranoquinoline derivatives in moderate yields. The synthesis is based on the Knoevenagel condensation of dimedone to various 2-chloroquinoline-3-carbaldehydes, followed by an

addition-elimination reaction. Additionally, NICS as quantitative measure for aromatic character and ^{1}H NMR and ^{13}C NMR chemical shifts of pyranoquinolines were also determined by DFT calculations with the help of full spectral analysis. The results show that NICS for the phenyl group of pyranoquinoline molecules **5** are less than that for benzene.

Supplementary Information

Supplementary information (copies of ^{1}H NMR, ^{13}C NMR and EI-MS of synthesized compounds (**3a**-**3d** and **5a**-**5d**) and DFT calculation information) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

We would like to acknowledge the financial support from Payame Noor University (PNU). We also are very grateful to Dr Zandi for his valuable suggestions on this paper to reach reasonable conclusions.

References

1. Bawa, S.; Kumar, S.; Drabu, S.; Kumar, R.; *J. Pharm. BioAllied Sci*. **2010**, *2*, 64; Ozyanik, M.; Demirci, S.; Bektas, H.; Demirbas, N.; Demirbas, A.; Kaaraoglu, S. A.; *Turk. J. Chem*. **2012**, *36*, 233; Chen, Y. L.; Chen, I. L.; Wang, T. C.; Han, C. H.; Tzeng, C. C.; *Eur. J. Med. Chem.* **2005**, *40*, 928; Leatham, P. A.; Bird, H. A.; Wright, V.; Seymour, D.; Gordon, A.; *Eur. J. Rheumatol. Inflammation* **1983**, *6*, 209; Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J.; *Bioorg. Med. Chem*. **2006**, *14*, 4600; Joshi, A. A.; Narkhede, S. S.; Viswanathan, C. L.; *Bioorg. Med. Chem. Lett*. **2005**, *15*, 73; Lahiri, D. K.; Farlow, M. R.; Hintz, N.; Utsuki, T.; Greig, N. H.; *Acta Neurol. Scand*. **2000**, *176*, 60.
2. Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Akberalib, P. M.; Shettyc, N. S.; *Bioorg. Med. Chem*. **2006**, *14*, 2040; Smirnov, R. F.; Tikhomirov, B. I.; Marinchenko, G. V.; Yakubchik, A. I.; *Polym. Sci. U.S.S.R.* **1973**, *15*, 832; Całus, S.; Gondek, E.; Danel, A.; Jarosz, B.; Pokładko, M.; Kityk, A. V.; *Mater. Lett.* **2007**, *61*, 3292; Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V.; *J. Org. Chem*. **2003**, *68*, 9371.
3. Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K.; Weston, H.; Scicinski, J.; Merritt, A.; Whittington, A.; Wyatt, P.; Taylor, N.; Green, D.; Bethell, R.; Madar, S.; Fenton, R. J.; Morley, P. J.; Pateman, T.; Beresford, A.; *J. Med. Chem*. **1998**, *41*, 787; Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W.; *Cancer Res*. **1975**, *35*, 3750; Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K.; *Mutat. Res*. **1997**, *395*, 47.
4. Tyurin, R. V.; Lukyanov, B. S.; Chernyshev, A. V.; Ozhogin, I. V.; Lukyanova, M. B.; *Chem. Heterocycl. Compd.* **2013**, *49*, 1251; Wang, X. S.; Zeng, Z. S.; Shi, D. Q.; Wei, X. Y.; Zong, Z. M.; *Synth. Commun*. **2004**, *34*, 3021.
5. Singh, B.; Chandra, A.; Upadhyay, S.; Singh, M. M. R.; Puerta, M. C.; Valerga, P.; *Tetrahedron Lett*. **2008**, *49*, 6423; Duan, X. F.; Zeng, J.; Zhang, Z. B.; Zi, G. F.; *J. Org. Chem*. **2007**, *72*, 10283; Puricelli, L.; Innocenti, G.; Delle Monache, G.; Caniato, R.; Filippini, R.; Cappelletti, E. M.; *Nat. Prod. Lett*. **2002**, *16*, 95; Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K.; *Biochem. Pharmacol*. **1992**, *44*, 1211; Mohmed, E. A.; *Chem. Pap*. **1994**, *48*, 261.
6. Clark, J. H.; Macquarrie, D. J.; *Org. Process Res. Dev*. **1997**, *1*, 149; Saeidian, H.; Sadeghi, A.; Mirjafary, Z.; Moghaddam, F. M.; *Synth. Commun*. **2008**, *38*, 2043; Blass, B. E.; *Tetrahedron* **2002**, *58*, 9301; Yadav, V. K.; Babu, K. G.; Mittal, M.; *Tetrahedron Lett*. **2001**, *57*, 7047; Moghaddam, F. M.; Saeidian, H.; Mirgafary, Z.; Sadeghi, A.; *Lett. Org. Chem*. **2007**, *8*, 576; Nazari, M.; Movassagh, B.; *Tetrahedron Lett*. **2009**, *50*, 1453; Bardajee, Gh. R.; *Tetrahedron Lett*. **2013**, *54*, 4937.; Zare, A.; Hasaninejad, A.; Moosavi-Zare, A. R.; Beyzavi, M. H.; Khalafi-Nezhad, A.; Pishahang, N.; Parsaee, Z.; Mahdavinasab, P.; Hayati, N.; *ARKIVOC* **2008**, *16*, 178.
7. Saeidian, H.; Mirgafary, Z.; Abdolmaleki, E.; Moradnia, F.; *Synlett* **2013**, *24*, 2127; Saeidian, H.; Abdoli, M.; Salimi, R.; *C. R. Chim.* **2013**, *16*, 1063; Moghaddam, F. M.; Koushki, B.; Saeidian, H.; Nourian, S.; Mirjafary, Z.; Kiamehr, M.; *Pure Appl. Chem*. **2011**, *83*, 709; Moghaddam, F. M.; Saeidian, H.; Mirjafary, Z.; Taheri, S.; Kheirjou, S.; *Synlett* **2009**, 1047.
8. Nyerges, M.; Pintér, A.; Virányi, A.; Blaskó, G.; Tőke, L.; *Tetrahedron* **2005**, *61*, 8199; Zahid, M.; Iaroshenko, V. O.; Saghyan, A. S.; Fischer, C.; Langer, P.; *Tetrahedron*, **2013**, *69*, 3451; Guo, M.; Zheng, C. J.; Song, M. X.; Wu, Y.; Sun, L. P.; Li, Y. J.; Liu, Y.; Piao, H. R.; *Bioorg. Med. Chem. Lett*. **2013**, *23*, 4358; Ilyn, A. P.; Loseva, M. V.; Vvedensky, V. Y.; Putsykina, E. B.; Tkachenko, S. E.; Kravchenko, D. V.; Khvat, A. V.; Krasavin, M. Y.; Ivachtchenko, A. V.; *J. Org. Chem*. **2006**, *71*, 2811.
9. Abdel-Wahab, B. F.; Khidre, R. E.; Farahat, A. A.; El-Ahl, A. A. S.; *ARKIVOC* **2012**, *1*, 211.
10. Brycki, B.; Kowalczyk, I.; Werner, J.; Borowiak, T.; Wolska, I.; *J. Mol. Struct*. **2006**, *791*, 137; Ghiasi, M.; Oskouie, A. A.; Saeidian, H.; *Carbohydr. Res*. **2012**, *348*, 47; Tormena, C. F.; Da Silva, G. V. J.; *Chem. Phys. Lett*. **2004**, *398*, 466.
11. Williams, R. V.; *Chem. Rev*. **2001**, *101*, 1185; Allen, D.; Tidwell, T. T.; *Chem. Rev*. **2001**, *101*, 1333; Katritzky, A. R.; Jug, K.; Oniciu, D. C.; *Chem. Rev*. **2001**, *101*, 1421.
12. Schleyer, P. V. R.; Manoharan, M.; Wang, Z. X.; Kiran, B.; Jiao, H.; Puchta, R.; Hammes, N. J. R. V. E.; *Org. Lett*. **2001**,

3, 2465; Kassaee, M. Z.; Jalalimanesh, N.; Musavi, S. M.; *J. Mol. Struct: THEOCHEM* **2007**, *816*, 153; Shaidaei, H. F. B.; Farkhonde, R.; Navideh, L. Gh.; *Comput. Theor. Chem*. **2011**, *963*, 525; Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. V. R.; *Chem. Rev*. **2005**, *105*, 3842.

13. Schleyer, P. V. R.; *Chem. Rev*. **2001**, *101*, 1115; Schleyer, P. V. R.; Jiao, H.; Van Eikema Hommes, N. J. R.; Malkin, V. G.; Malkina, O.; *J. Am. Chem. Soc*. **1997**, *119*, 12669.
14. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; *Gaussian 03, Revision E.01*; Gaussian, Inc., Wallingford, CT, 2004.
15. Wolinski, K.; Hilton, J. F.; Pulay, P.; *J. Am. Chem. Soc*. **1990**, *112*, 8251.
16. Schleyer, P. V. R.; Manoharan, M.; Jiao, H.; Stahl, F.; *Org. Lett*. **2001**, *3*, 3643.

Submitted: March 12, 2014
Published online: May 16, 2014

J. Braz. Chem. Soc., Vol. 25, No. 7, S1-S18, 2014.
Printed in Brazil - ©2014 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Supplementary Information

Efficient Synthesis of Novel Pyranoquinoline Derivatives from Simple Acetanilide Derivatives: Experimental and Theoretical Study of their Physicochemical Properties using DFT Calculations

Zohreh Mirjafary,[a] Hamid Saidian,*[b] Morteza Sahandi[b] and Leila Shojaei[b]

[a]Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran

[b]Department of Science, Payame Noor University (PNU), PO Box 19395-4697, Tehran, Iran

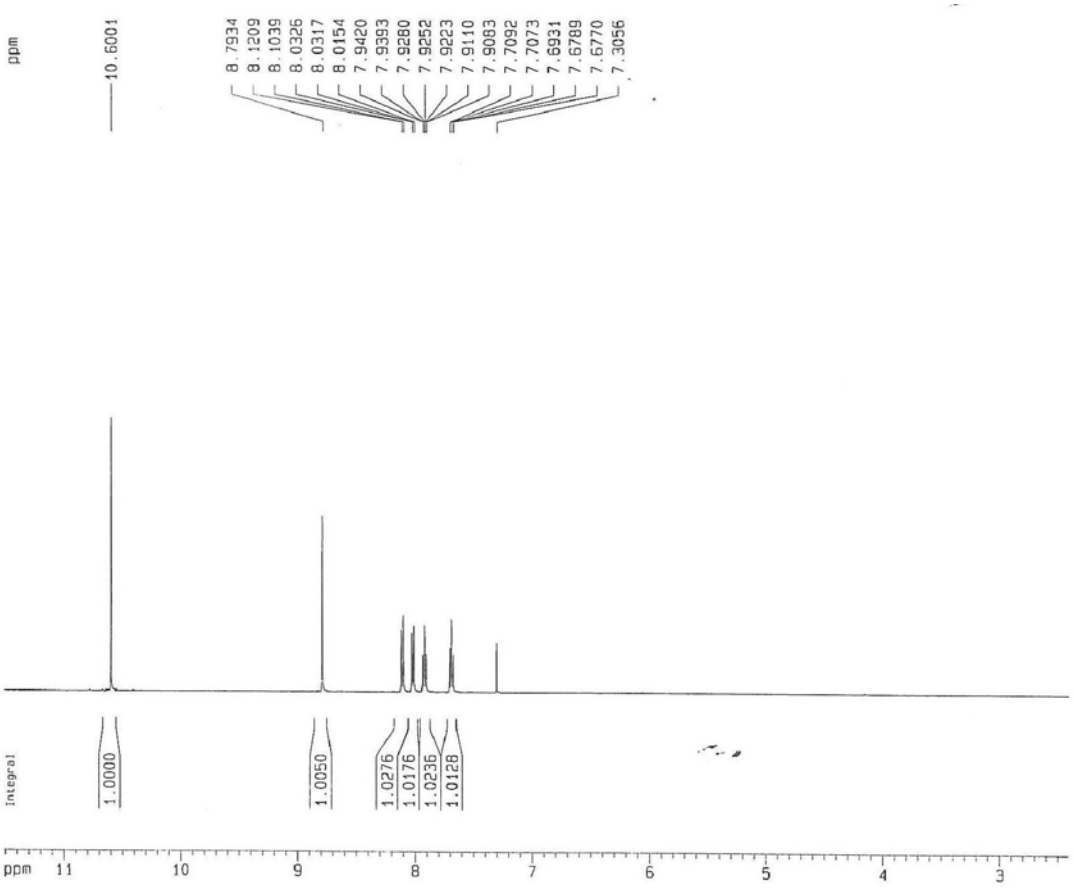


Figure S1. ^{1}H NMR of spectrum **3a** ($CDCl_3$, 500 MHz).

*e-mail: h_porkaleh@yahoo.com

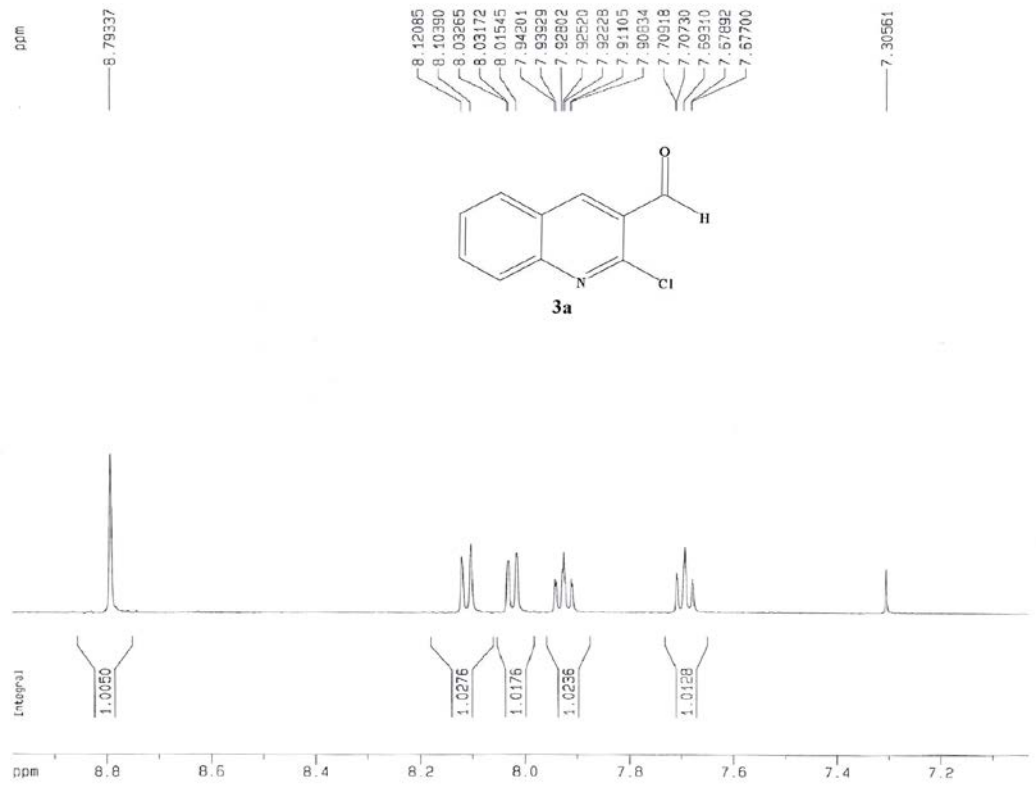


Figure S2. ^{1}H NMR spectrum of **3a** ($CDCl_3$, 500 MHz).

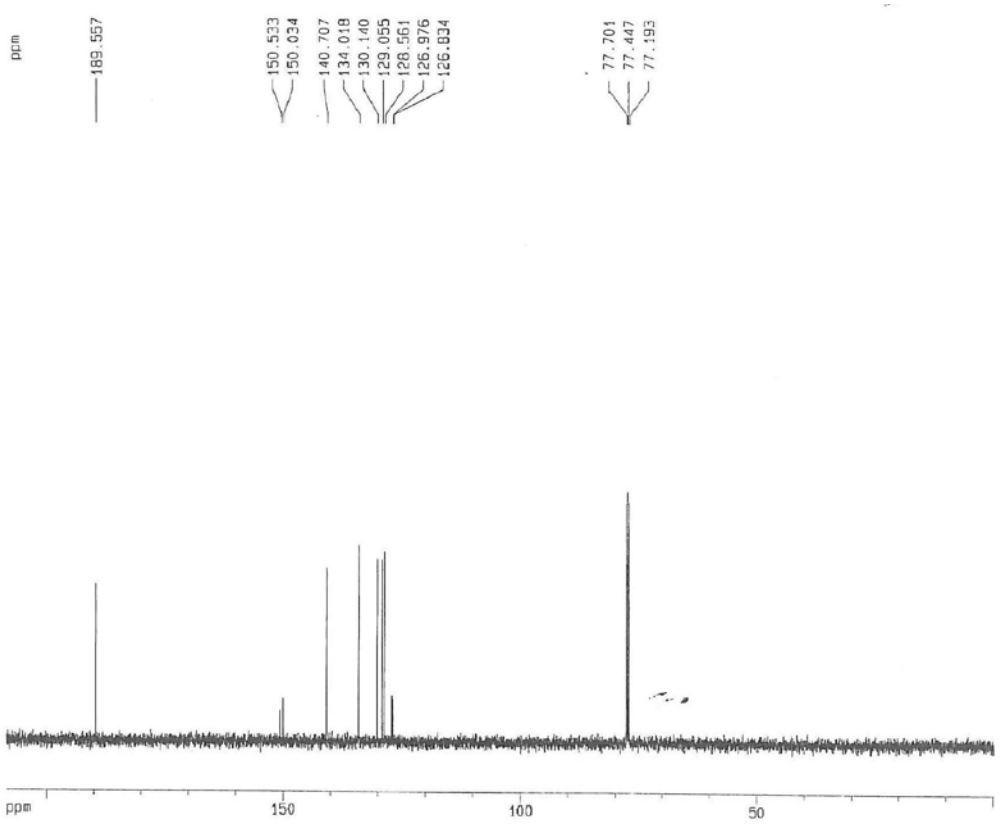


Figure S3. ^{13}C NMR spectrum of **3a** ($CDCl_3$, 125 MHz).

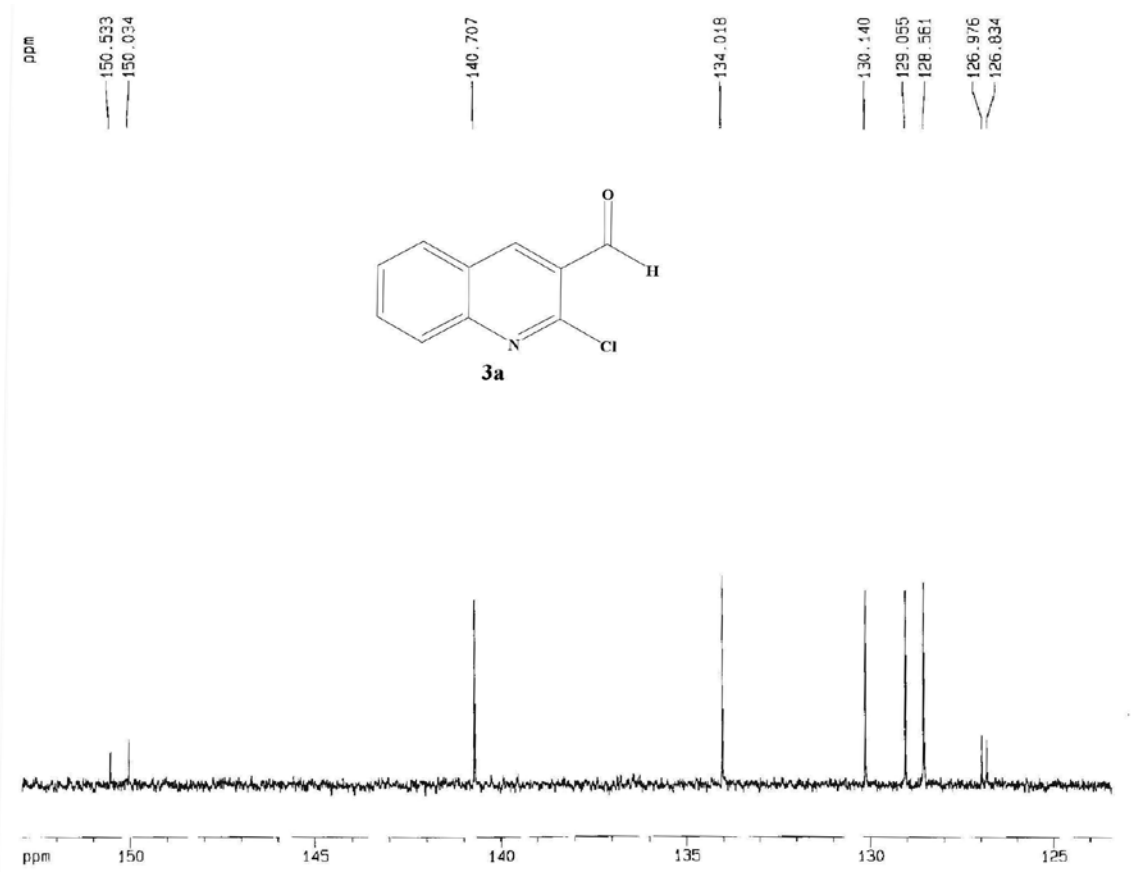


Figure S4. ^{13}C NMR spectrum of **3a** ($CDCl_3$, 125 MHz).

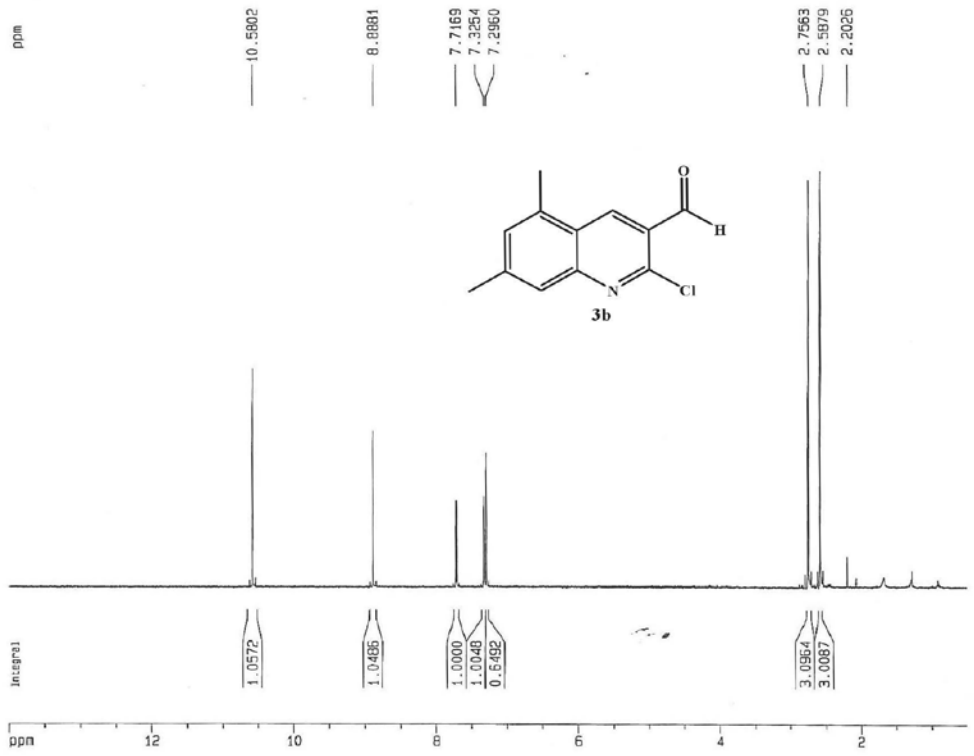


Figure S5. ^{1}H NMR spectrum of **3b** ($CDCl_3$, 500 MHz).

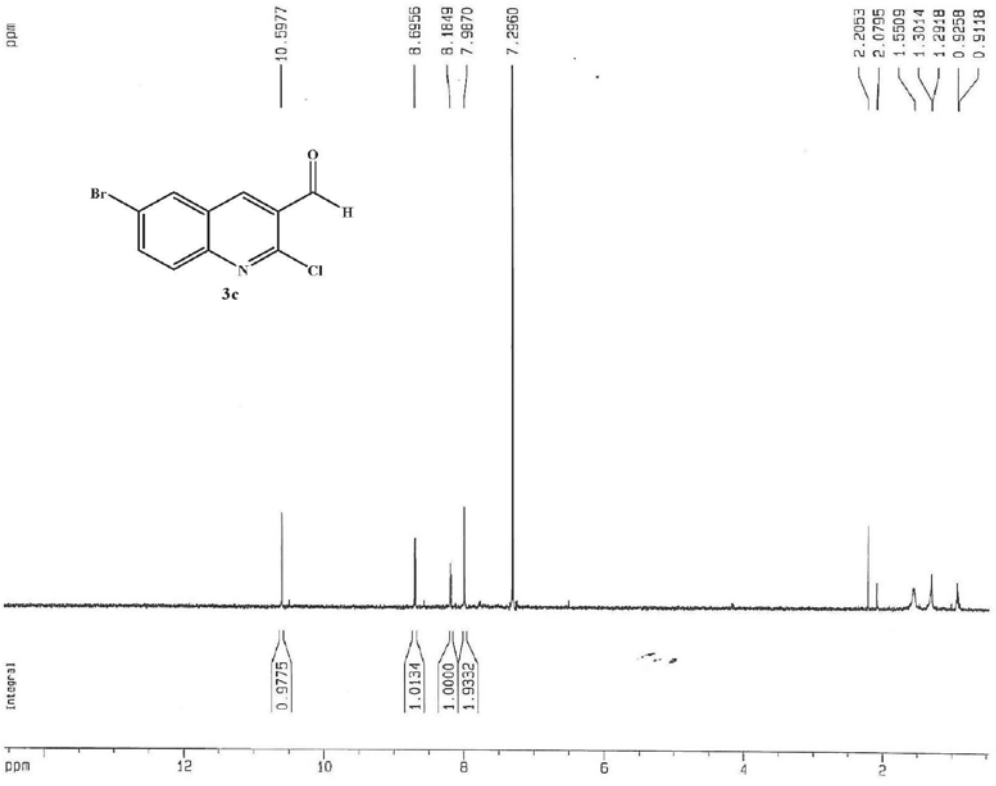


Figure S6. ^{1}H NMR spectrum of **3c** ($CDCl_3$, 500 MHz).

Figure S7. ^{1}H NMR spectrum of **3d** ($CDCl_3$, 500 MHz).

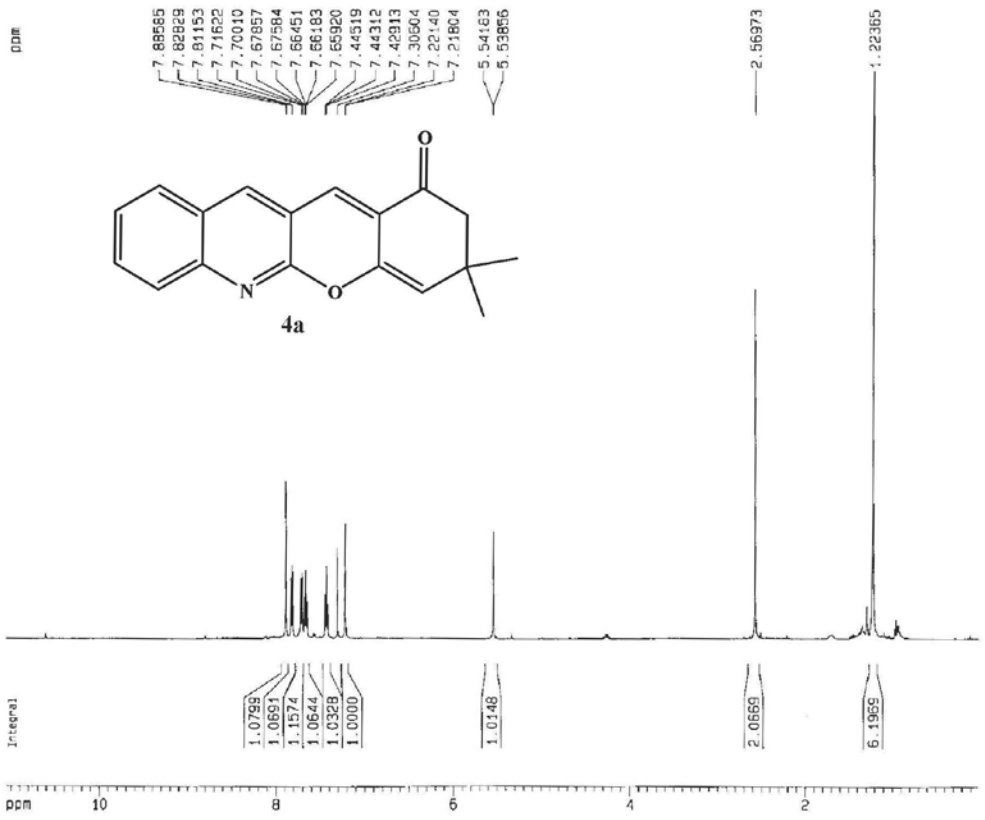


Figure S8. ^{1}H NMR spectrum of **4a** ($CDCl_3$, 500 MHz).

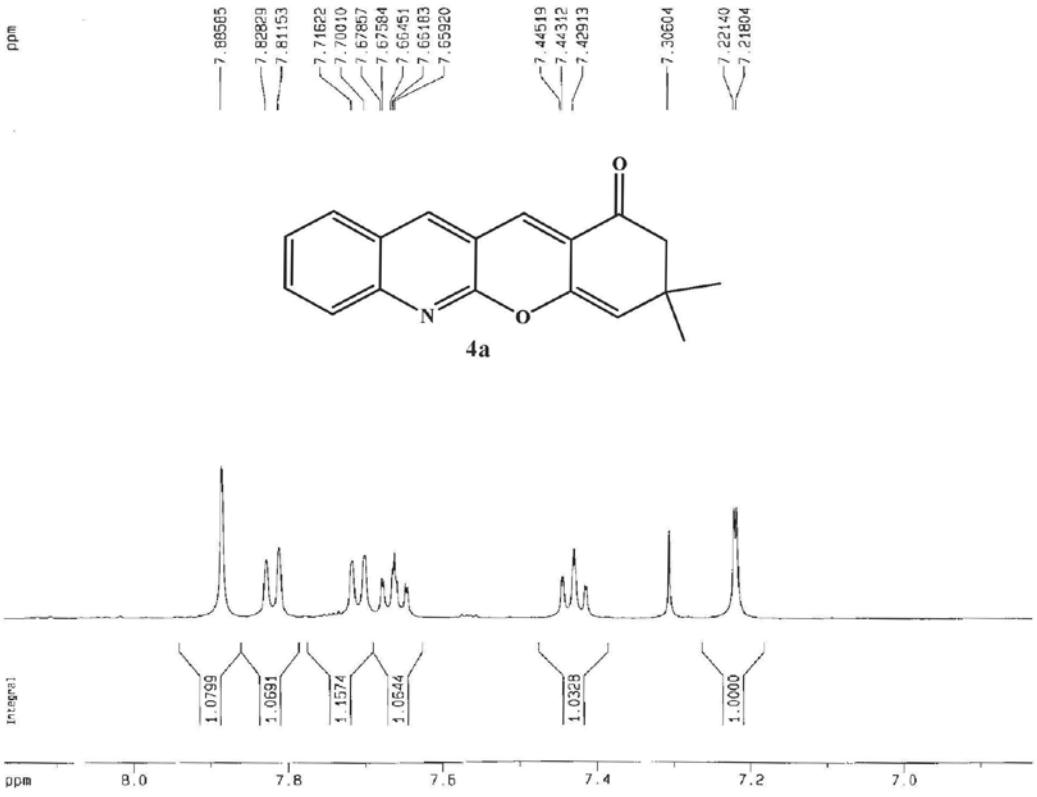


Figure S9. ^{1}H NMR spectrum of **4a** ($CDCl_3$, 500 MHz).

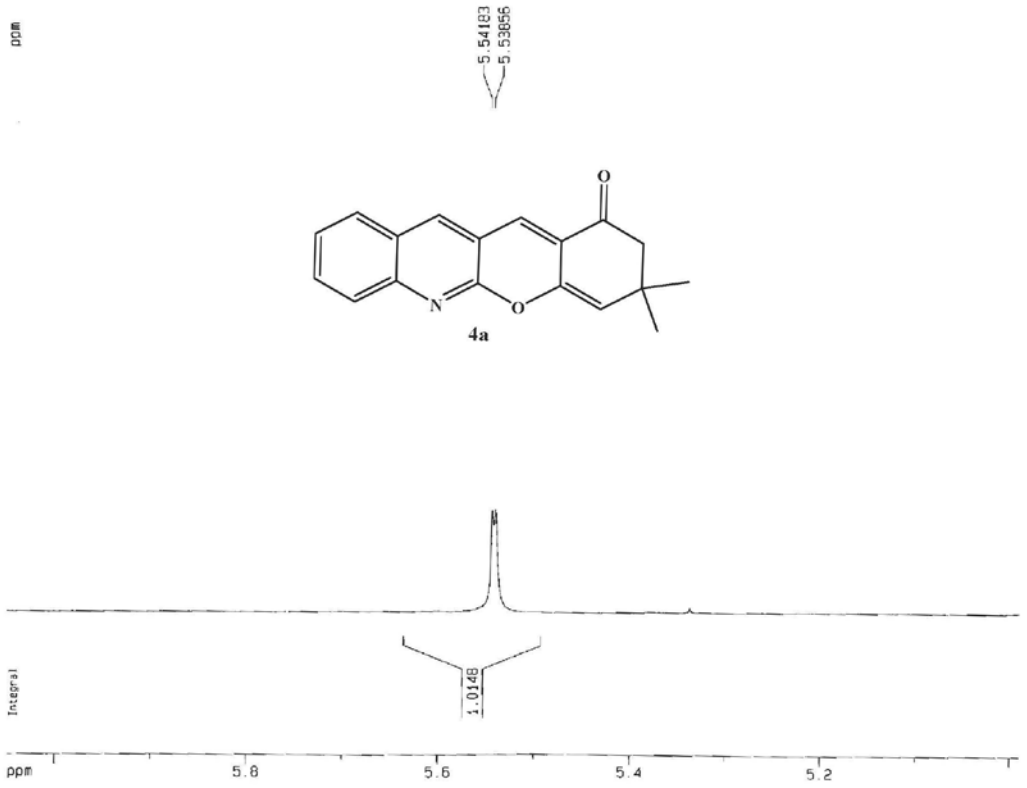


Figure S10. ^{1}H NMR spectrum of **4a** ($CDCl_3$, 500 MHz).

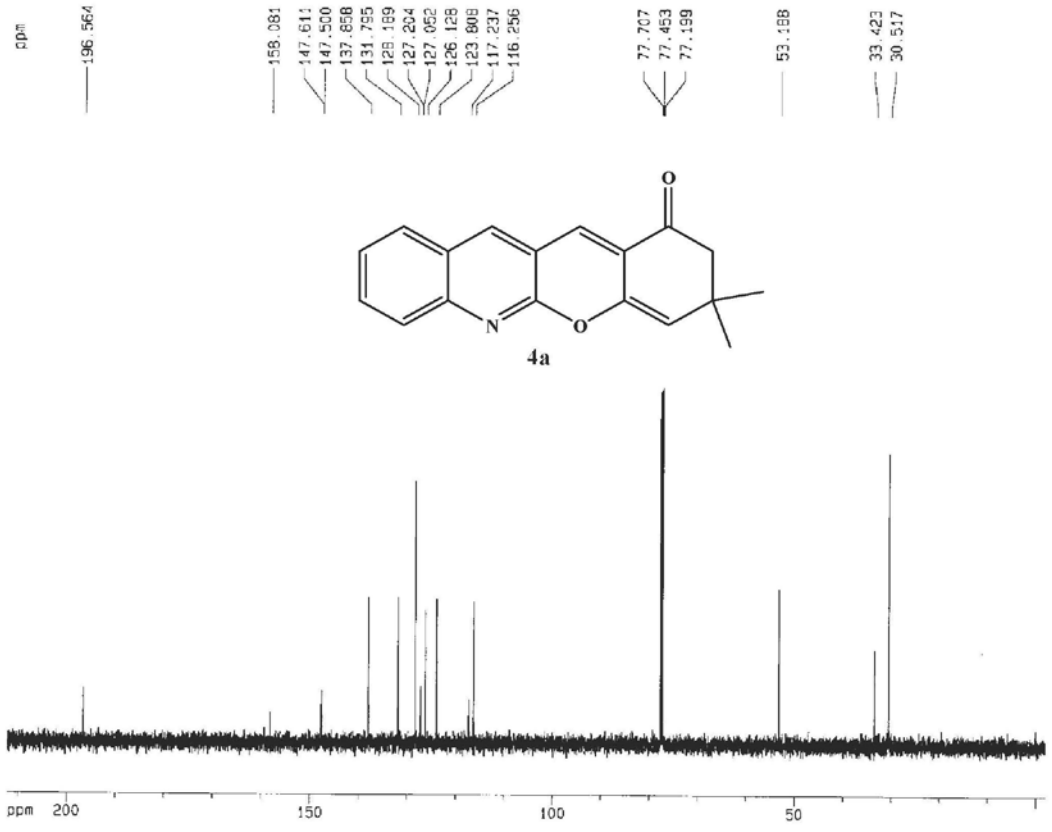


Figure S11. ^{13}C NMR spectrum of **4a** ($CDCl_3$, 125 MHz).

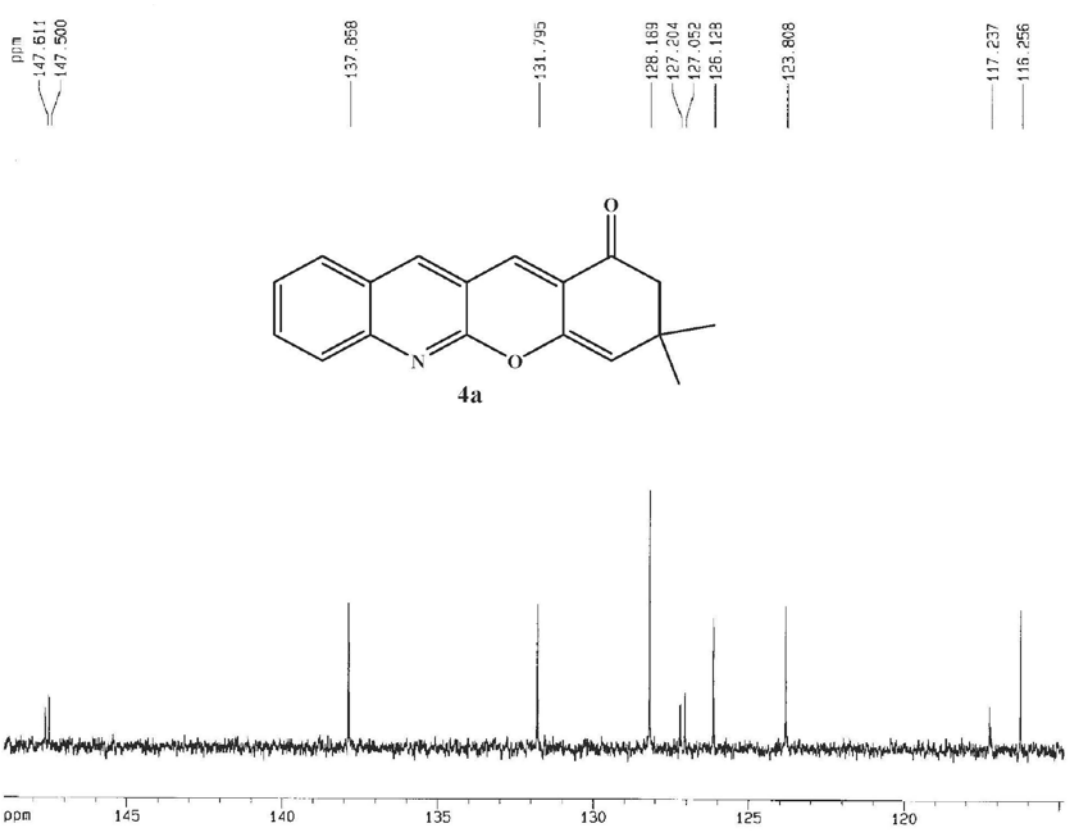


Figure S12. ^{13}C NMR spectrum of **4a** ($CDCl_3$, 125 MHz).

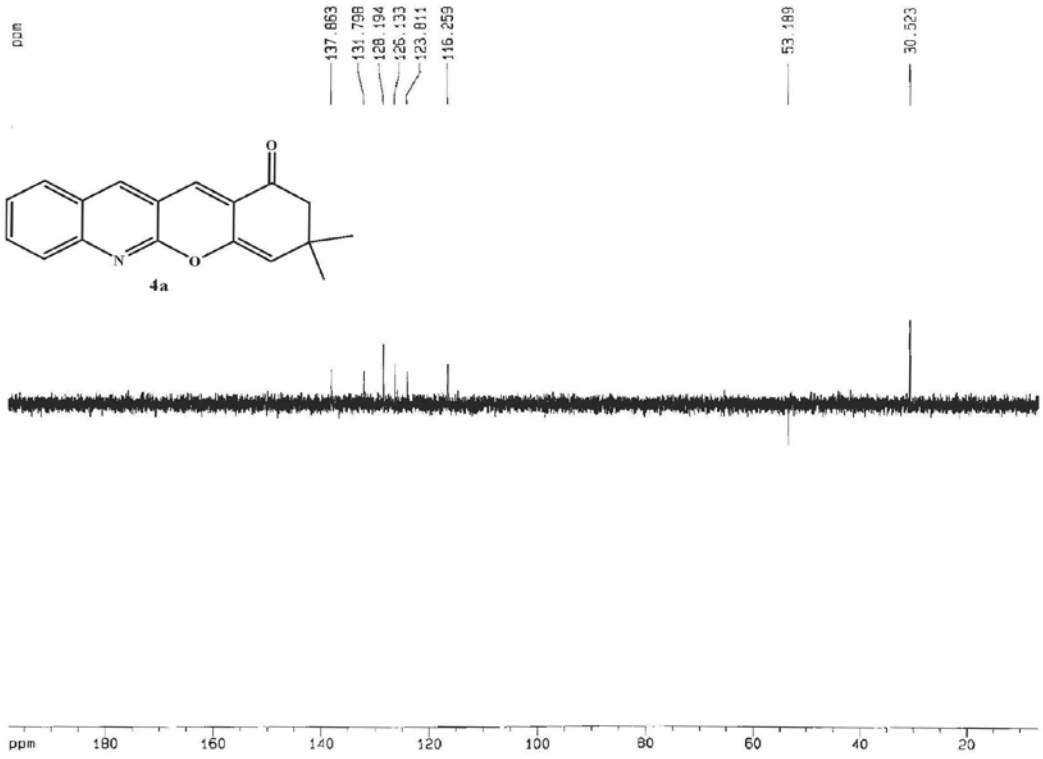


Figure S13. ^{13}C NMR (DEPT 135) spectrum of **4a** ($CDCl_3$, 125 MHz).

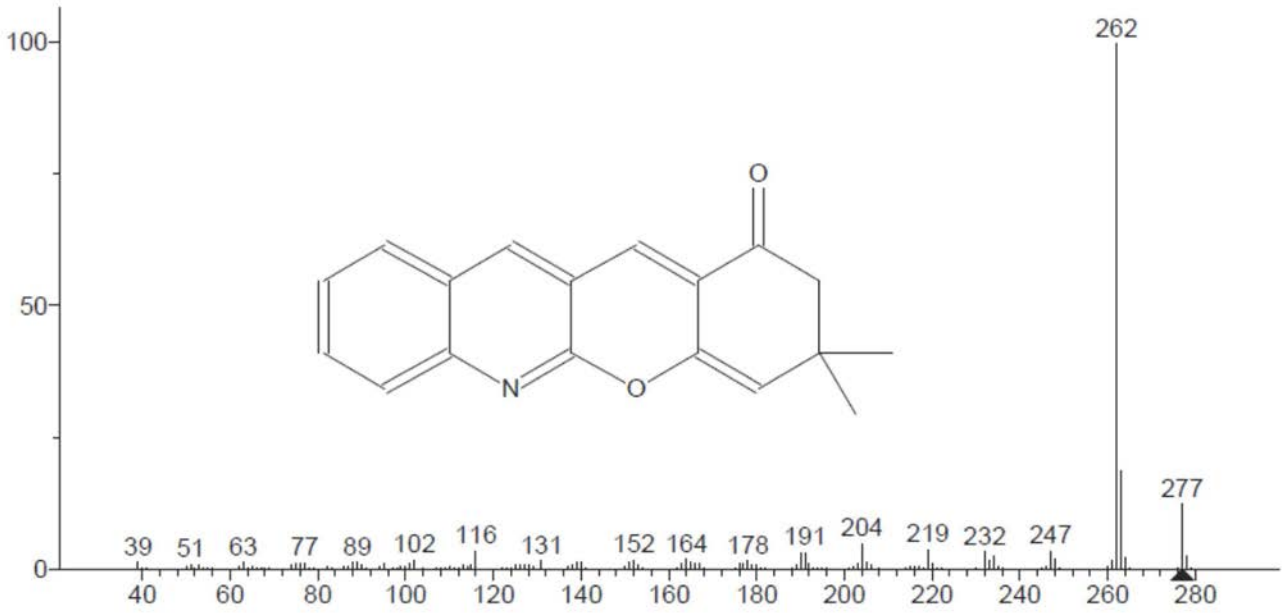


Figure S14. EI-MS spectrum of **4a**.

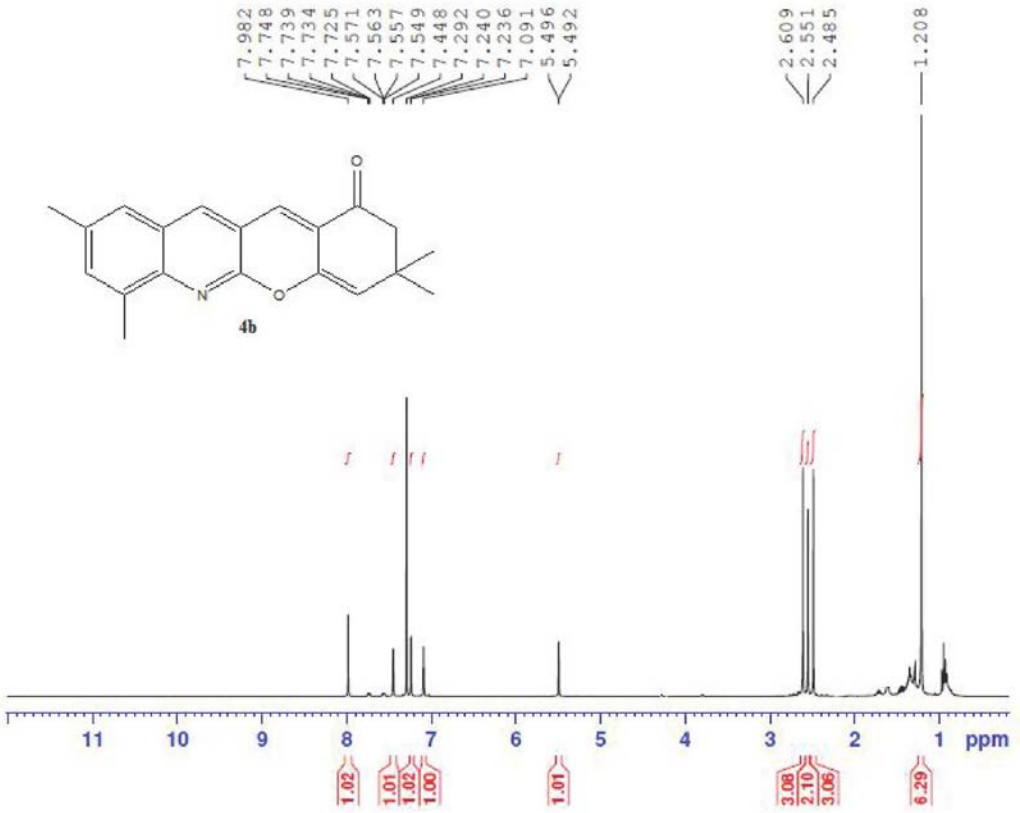


Figure S15. ^{1}H NMR spectrum of **4b** ($CDCl_3$, 400 MHz).

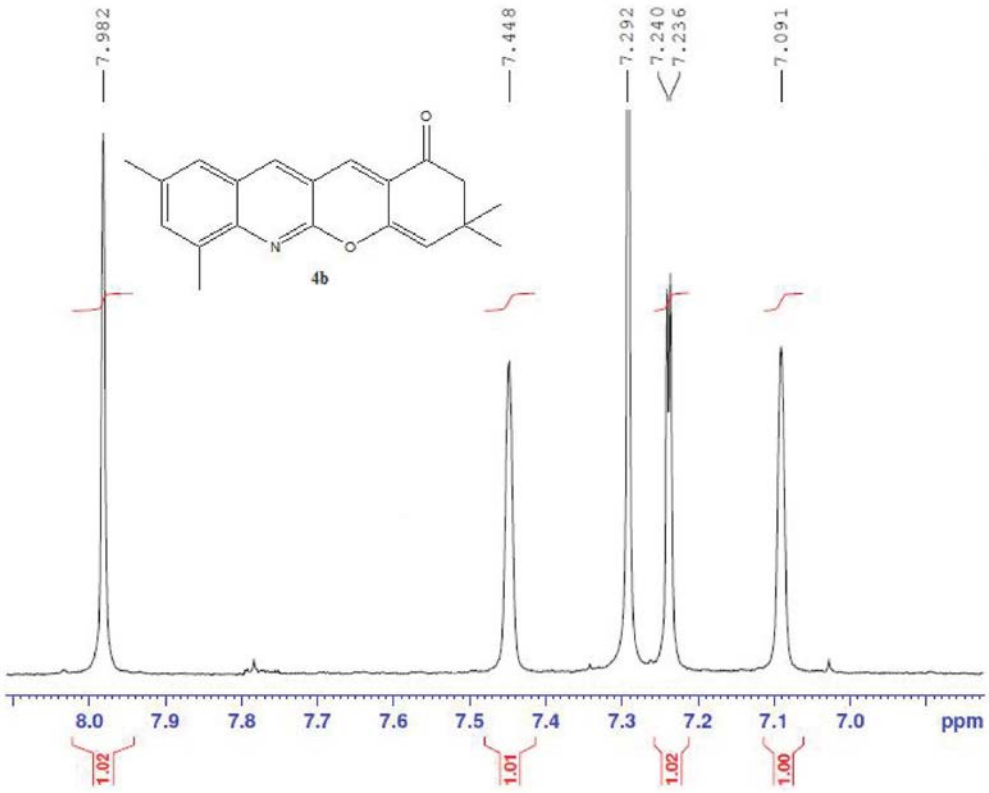


Figure S16. ^{1}H NMR spectrum of **4b** ($CDCl_3$, 400 MHz).

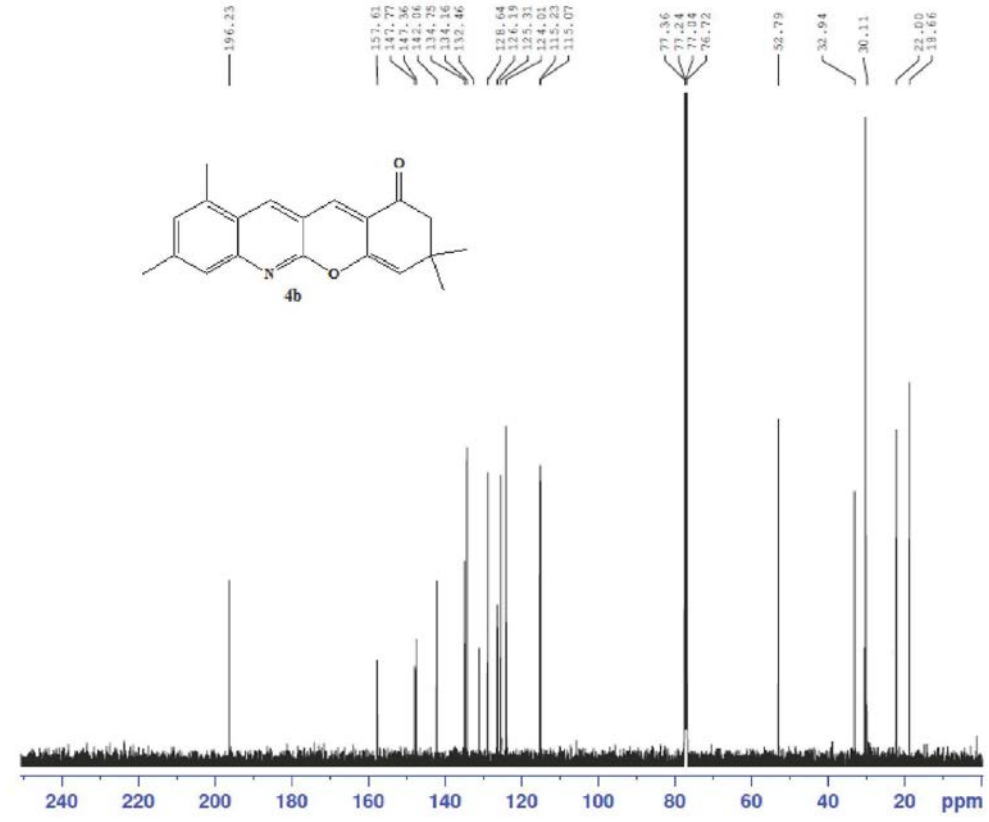


Figure S17. ^{13}C NMR spectrum of **4b** ($CDCl_3$, 100 MHz).

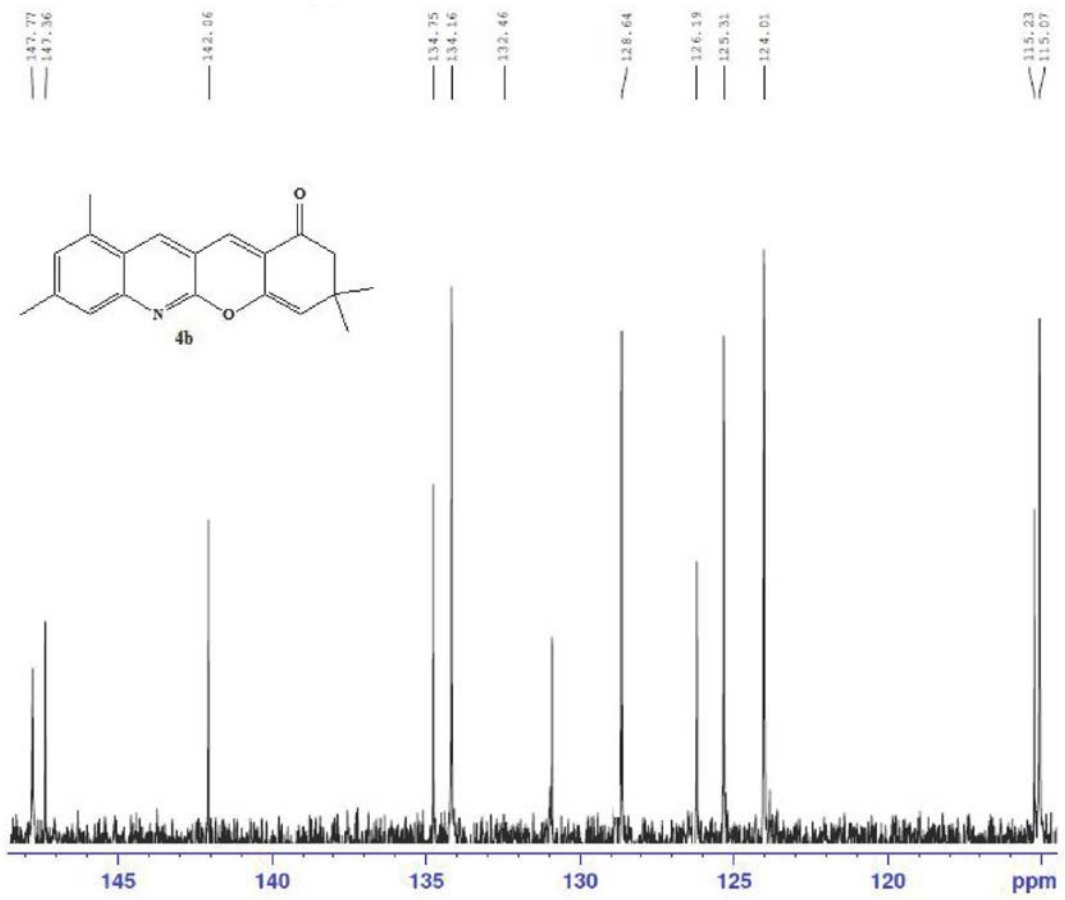


Figure S18. ^{13}C NMR spectrum of **4b** ($CDCl_3$, 100 MHz).

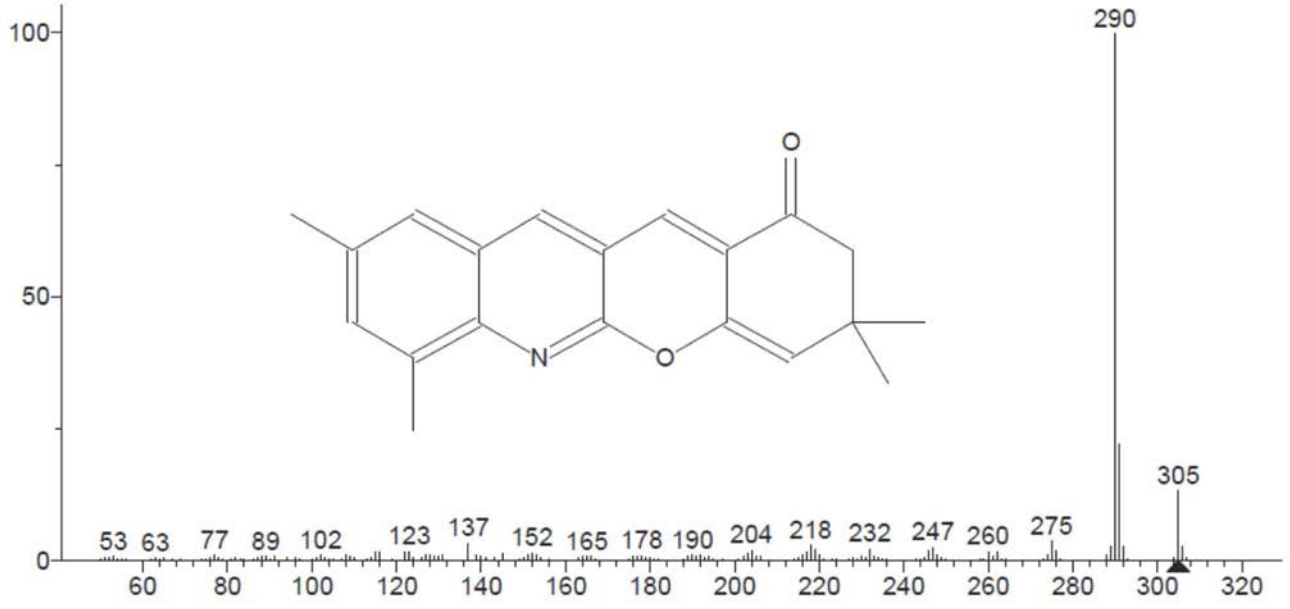


Figure S19. EI-MS spectrum of **4b**.

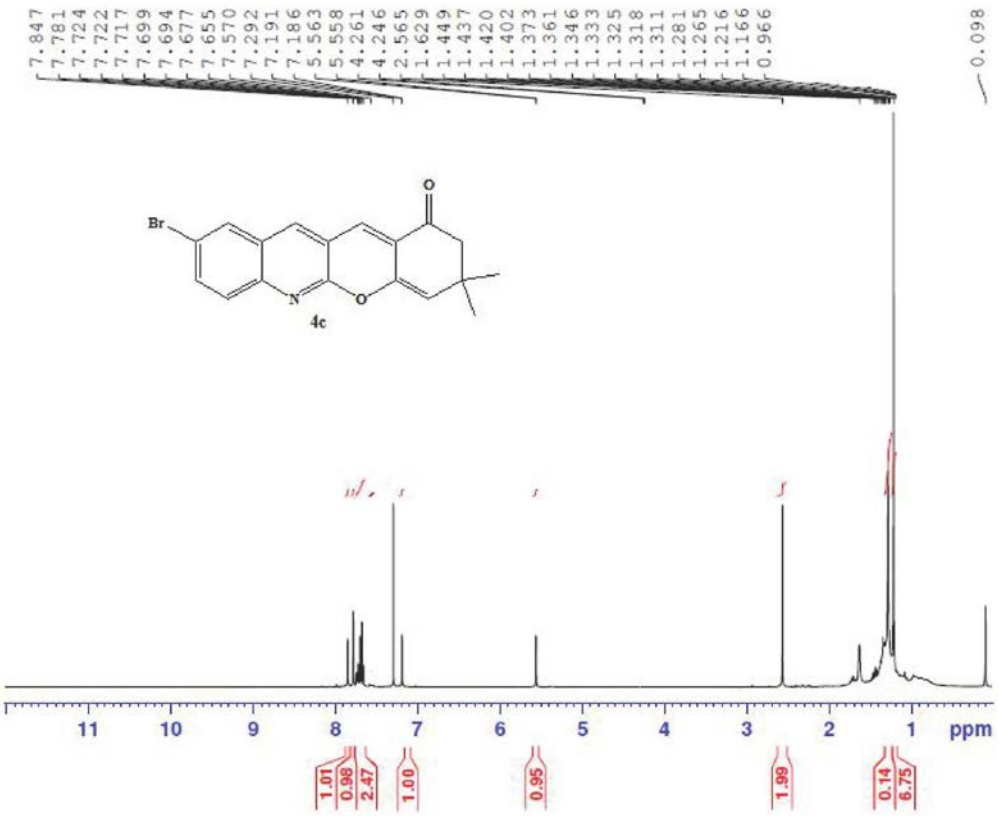


Figure S20. ^{1}H NMR spectrum of **4c** ($CDCl_3$, 400 MHz).

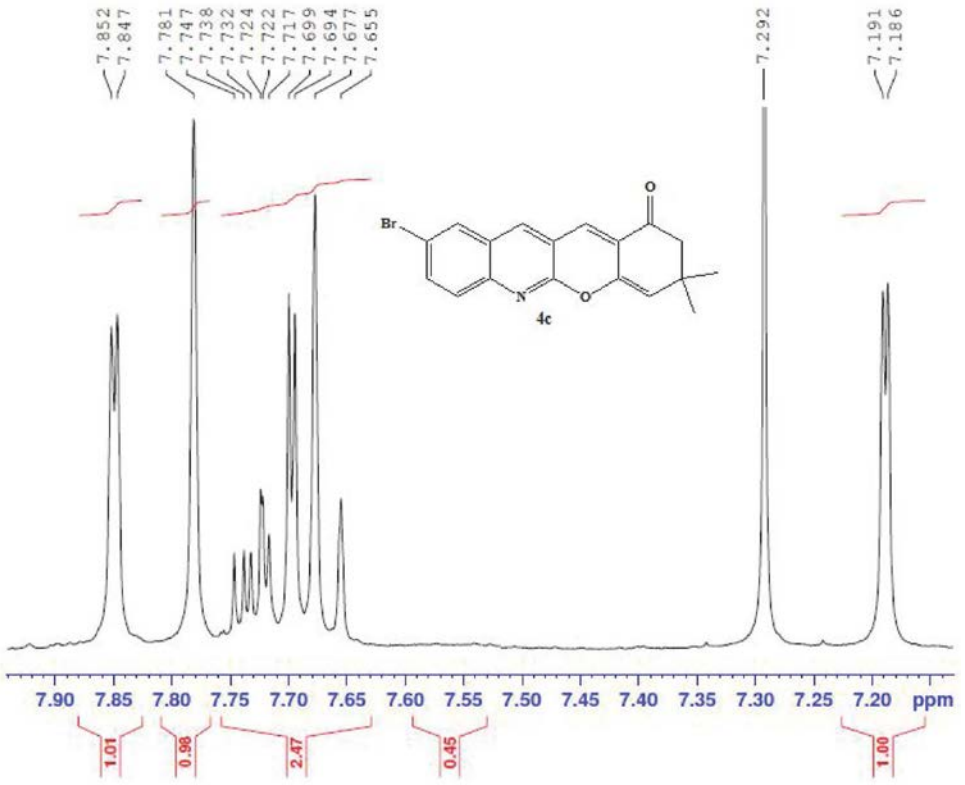


Figure S21. ^{1}H NMR spectrum of **4c** ($CDCl_3$, 400 MHz).

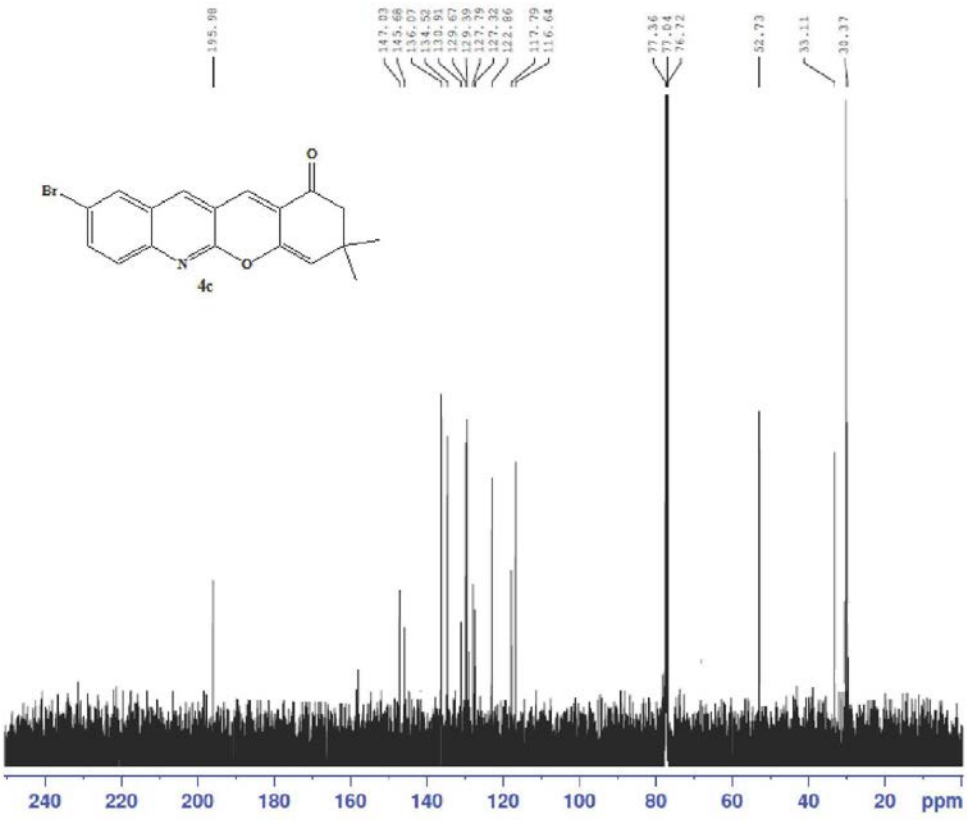


Figure S22. ^{13}C NMR spectrum of **4c** ($CDCl_3$, 100 MHz).

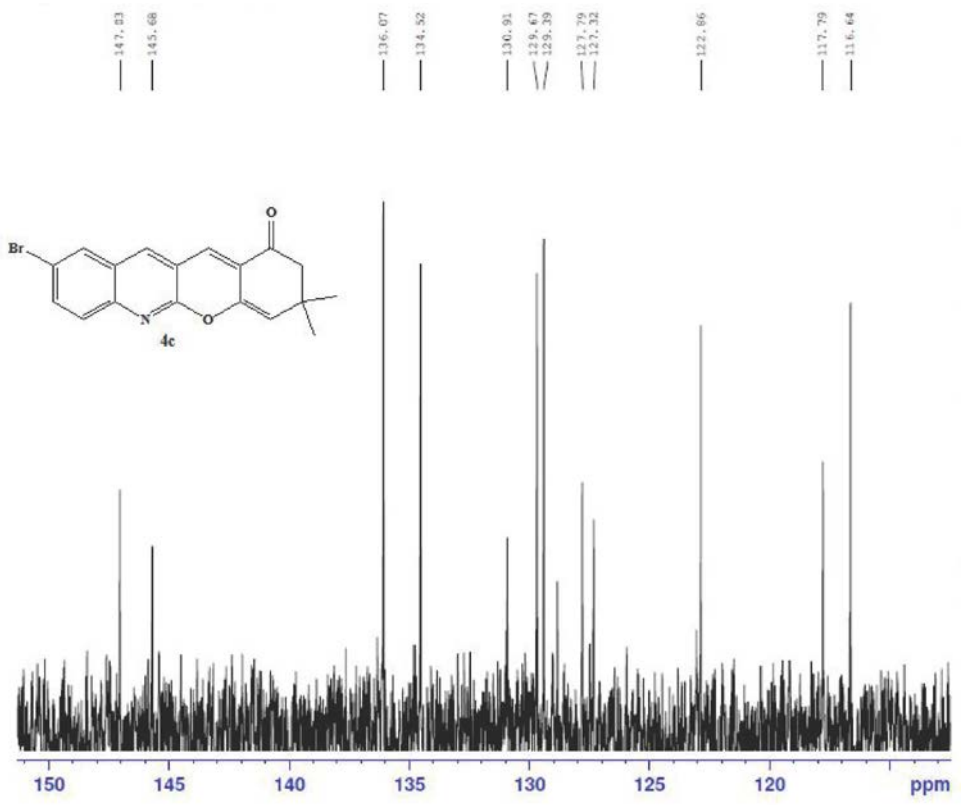


Figure S23. ^{13}C NMR spectrum of **4c** ($CDCl_3$, 100 MHz).

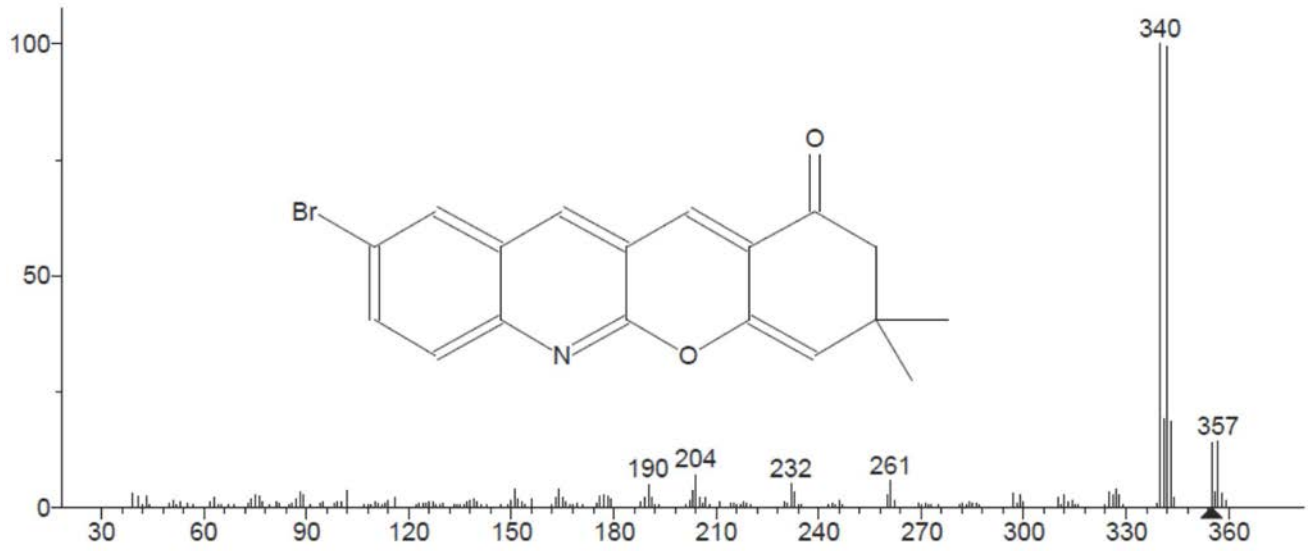


Figure S24. EI-MS spectrum of **4c**.

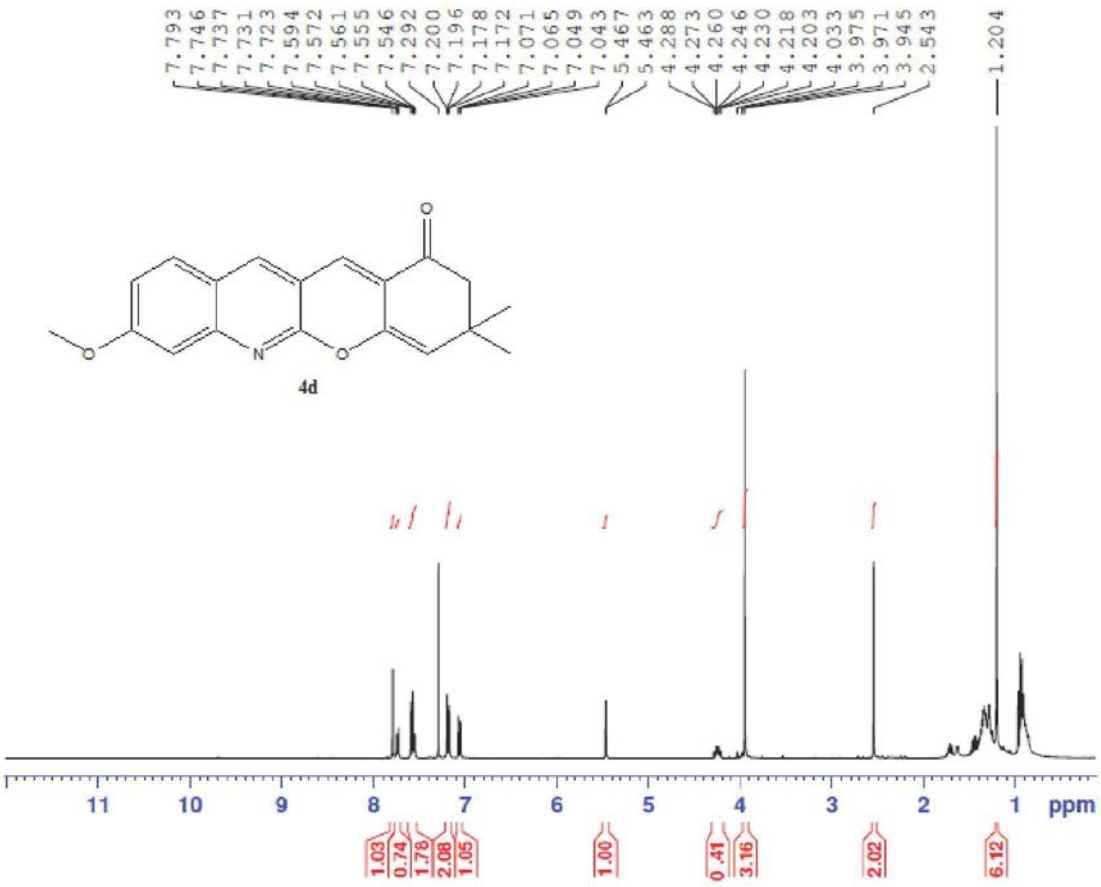


Figure S25. ^{1}H NMR spectrum of **4d** ($CDCl_3$, 400 MHz).

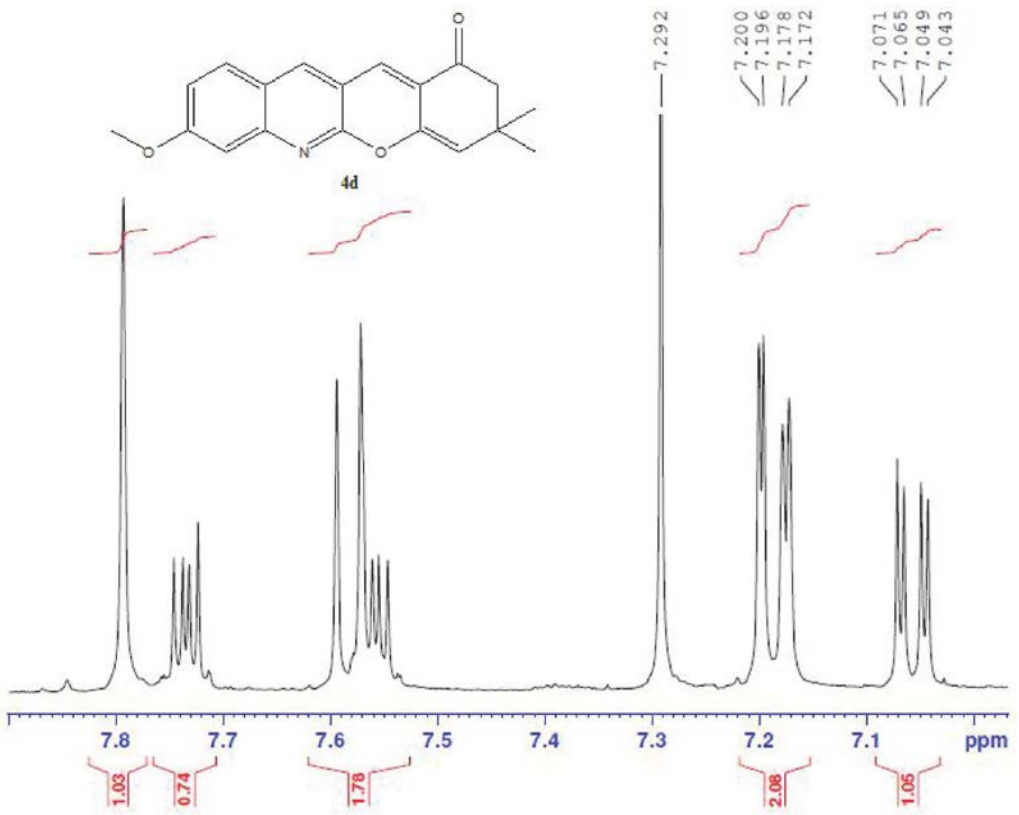


Figure S26. ^{1}H NMR spectrum of **4d** ($CDCl_3$, 400 MHz).

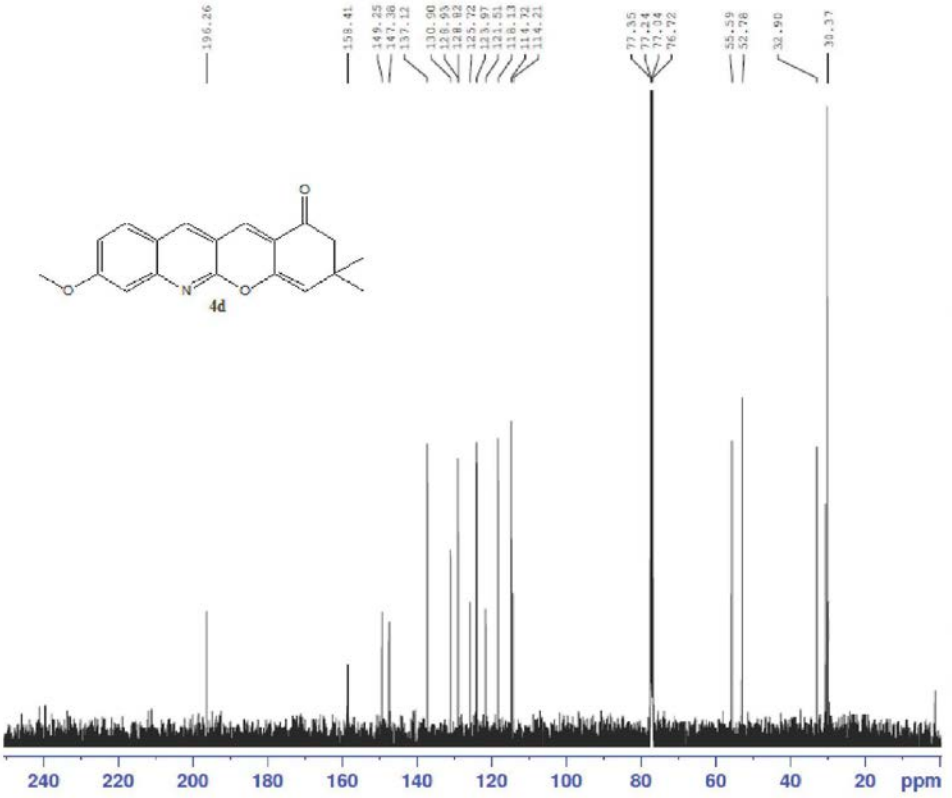


Figure S27. ^{13}C NMR spectrum of **4d** ($CDCl_3$, 100 MHz).

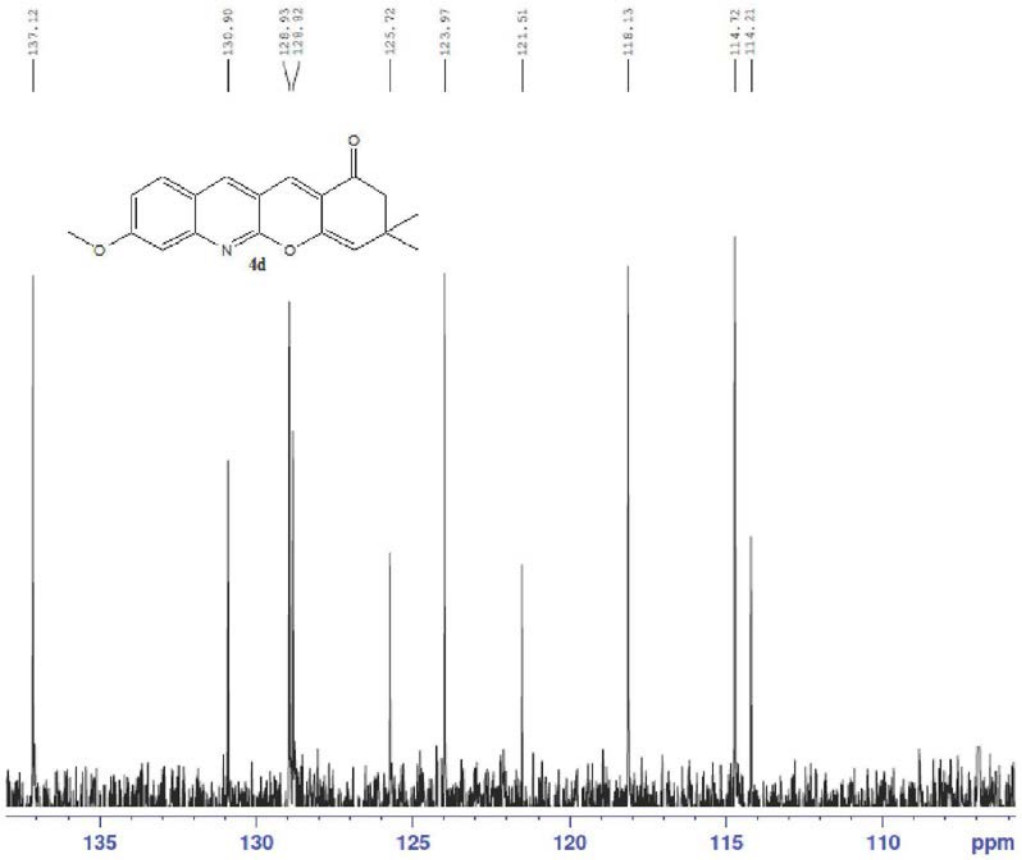


Figure S28. ^{13}C NMR spectrum of **4d** ($CDCl_3$, 100 MHz).

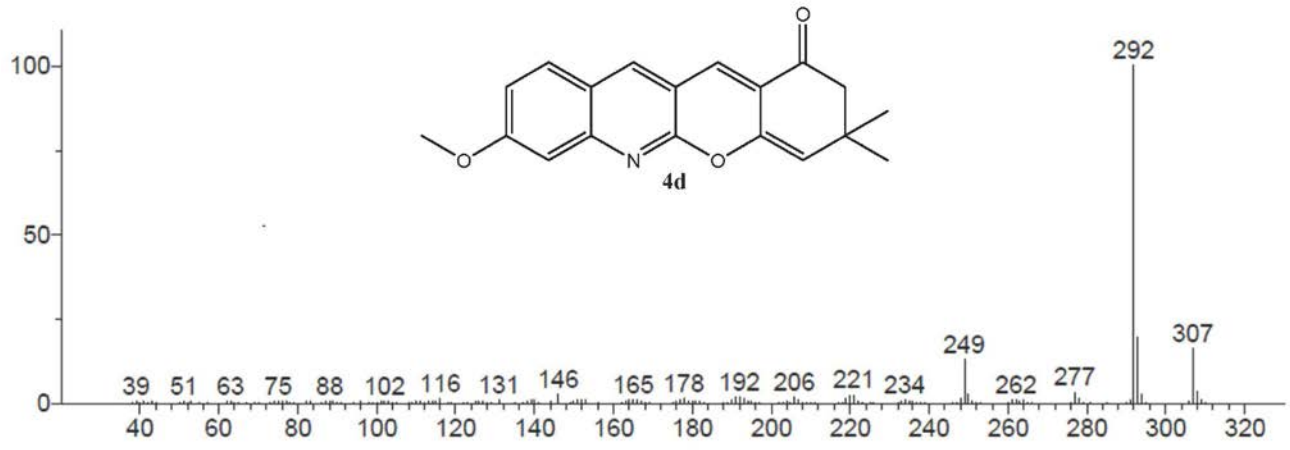


Figure S29. EI-MS spectrum of **4d**.

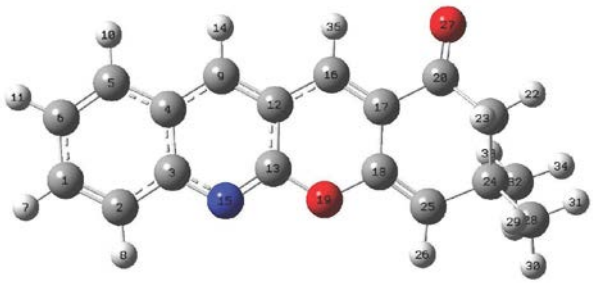


Figure S30. Atom numbering in accordance with molecular structure of pyranoquinoline **5a**.

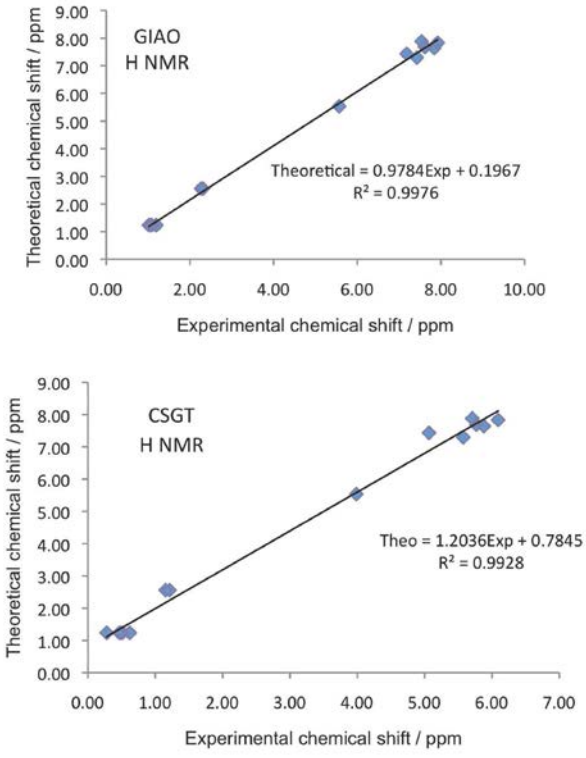


Figure S31. Correlation coefficient for ^{1}H NMR chemical shifts in GIAO and CSGT methods for pyranoquinoline **5a.**

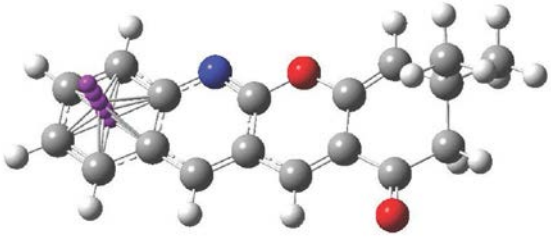


Figure S32. NMR calculations with molecular structure of pyranoquinoline **5a**.

Table S1. Symbolic Z-matrix: charge = 0, multiplicity = 1

C	5.58978	−1.00942	0.03819
C	4.33858	−1.57814	−0.01819
C	3.18587	−0.76528	−0.02234
C	3.34039	0.65245	0.03151
C	4.64035	1.20702	0.08847
C	5.74518	0.39132	0.09207
H	6.46684	−1.64214	0.04155
H	4.20461	−2.6495	−0.0592
C	2.16352	1.43239	0.0218
H	4.75061	2.28298	0.12902
H	6.73674	0.8196	0.13609
C	0.92876	0.82828	−0.03219
C	0.90737	−0.60511	-0.07651
H	2.23179	2.51264	0.05578
N	1.95798	−1.36227	−0.07596
C	−0.32426	1.53273	−0.06117
C	−1.48604	0.84859	−0.10623
C	−1.49516	−0.60227	−0.09691
O	−0.28019	−1.27097	−0.12881
C	−2.8002	1.55224	−0.17138
C	-3.98094	0.6916	−0.56567
H	−4.89626	1.2378	−0.34296
H	−3.91871	0.58645	−1.65479
C	−3.99208	−0.72161	0.06103
C	−2.61332	−1.33544	−0.02363
H	−2.52504	−2.41288	0.02598
O	−2.89644	2.7466	0.02855
C	−4.99623	−1.60222	−0.7036
H	−4.70869	−1.70921	−1.74999
H	−5.0479	−2.59967	−0.26455
H	−5.99685	−1.16871	−0.66713
C	−4.42511	−0.63359	1.54333
H	−3.76322	0.02019	2.1119
H	−5.44168	−0.24399	1.62466
H	−4.40191	−1.61836	2.01084
H	−0.34212	2.6144	−0.0548

Table S2. Computed B3LYP/6-31+G(d,p) ^{1}H and ^{13}C NMR chemical shifts (ppm) for pyranoquinoline **5a** and TMS

Atom	Pyranoquinoline **5a**		TMS	
	GIAO	CSGT	GIAO	CSGT
C1	65.5686	63.0161	191.3637	193.7630
C2	66.0551	63.6816	191.3637	193.7630
C3	46.5088	43.6895	191.3637	193.7630
C4	66.6606	64.7685	191.3637	193.7630
C5	68.7895	65.5050	191.3637	193.7630
C6	71.4025	68.8041	191.3637	193.7630
C9	59.9738	55.7594	191.3637	193.7630
C12	69.4734	73.4249	191.3637	193.7630
C13	37.4360	34.1288	191.3637	193.7630
C16	70.7957	65.3104	191.3637	193.7630
C17	66.0421	63.8793	191.3637	193.7630
C18	45.4116	41.1712	191.3637	193.7630
C20	0.5899	-1.0235	191.3637	193.7630
C21	137.8278	138.5408	191.3637	193.7630
C24	154.9028	159.3515	191.3637	193.7630
C25	79.5548	77.2708	191.3637	193.7630
C28	160.7181	161.6168	191.3637	193.7630
C32	162.3555	163.0471	191.3637	193.7630
H7	23.7831	23.5501	31.6210	29.4288
H8	23.7009	23.3384	31.6210	29.4288
H10	24.0046	23.6613	31.6210	29.4288
H11	24.1978	23.8558	31.6210	29.4288
H14	24.0849	23.7225	31.6210	29.4288
H22	29.3568	28.2171	31.6210	29.4288
H23	29.3125	28.2756	31.6210	29.4288
H26	26.0548	25.4430	31.6210	29.4288
H29	30.4356	28.9536	31.6210	29.4288
H30	30.4231	28.8072	31.6210	29.4288
H31	30.6055	28.9489	31.6210	29.4288
H33	30.5519	28.9604	31.6210	29.4288
H34	30.5932	29.1500	31.6210	29.4288
H35	30.5309	28.9178	31.6210	29.4288
H36	24.4410	24.3643	31.6210	29.4288

Table S3. Computed B3LYP/6-31+G(d,p) ^{1}H and ^{13}C NMR chemical shifts for pyranoquinoline **5a** relative to TMS

Atom	Chemical shifts / ppm	
	GIAO	CSGT
C1	125.80	130.75
C2	125.31	130.08
C3	144.85	150.07
C4	124.70	128.99
C5	122.57	128.26
C6	119.96	124.96
C9	131.39	138.00
C12	121.89	120.34
C13	153.93	159.63
C16	120.57	128.45
C17	125.32	129.88
C18	145.95	152.59
C20	190.77	194.79
C21	53.54	55.22
C24	36.46	34.41
C25	111.81	116.49
C28	30.65	32.15
C32	29.01	30.72
H7	7.84	5.88
H8	7.92	6.09
H10	7.62	5.77
H11	7.42	5.57
H14	7.54	5.71
H22	2.26	1.21
H23	2.31	1.15
H26	5.57	3.99
H29	1.19	0.48
H30	1.20	0.62
H31	1.02	0.48
H33	1.07	0.47
H34	1.03	0.28
H35	1.09	0.51
H36	7.18	5.06

Table S4. # B3LYP/6-31+G** NMR, Symbolic Z-matrix: charge = 0, multiplicity = 1 for **4c**

C	−4.27896	−0.14203	−0.01106
C	−4.03364	−1.53332	−0.05842
C	−2.73505	−1.99991	−0.09396
C	−1.64273	−1.09916	−0.08352
C	−1.90796	0.30717	−0.03557
C	−3.24821	0.77089	0.00051
N	−0.37312	−1.60563	−0.11793
C	0.62226	−0.76666	−0.1049
C	0.49238	0.66581	−0.06338
C	−0.78999	1.1788	−0.02878
O	1.85726	−1.34361	−0.14032
C	1.69403	1.46409	−0.07854
Br	−6.08609	0.46693	0.03666
C	2.9084	0.86213	−0.11168
C	3.02388	−0.58869	−0.098
C	4.19712	−1.24284	−0.0159
C	5.52774	−0.52397	0.08506
C	5.41827	0.88591	−0.5494
C	4.17154	1.65975	−0.16864
C	6.6087	−1.33045	−0.66321
O	4.17682	2.86742	0.02322
C	5.93189	−0.39816	1.5766
H	−4.86799	−2.22587	−0.06623
H	−2.52157	−3.06295	−0.13026
H	−3.4478	1.83686	0.03697
H	−0.94079	2.25508	0.00216
H	1.63219	2.54856	−0.07536
H	4.18774	−2.32839	0.03318
H	6.29258	1.50093	−0.31809
H	5.37583	0.7731	−1.64355
H	7.57637	−0.81828	−0.61685
H	6.34311	−1.46671	−1.717
H	6.7325	−2.32245	−0.21452
H	6.91875	0.0704	1.67024
H	5.97685	−1.38487	2.04927
H	5.21143	0.2079	2.13589
Bq	−2.96439	−0.57828	−0.04387
Bq	−2.9761	−0.63509	0.45275
Bq	−2.9761	−0.63509	0.95275
Bq	−2.9761	−0.63509	1.45275
Bq	−2.9761	−0.63509	1.95275